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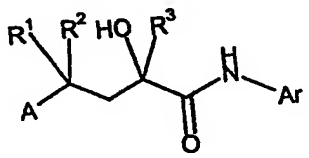
(54) Title: NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

(57) Abstract: The invention pertains to the use of compounds with general formula I as nonsteroidal anti-inflammatory agents, as well as to methods for the production of these and other selected compounds.



(I)

Nonsteroidal Anti-inflammatory Agents

The present invention pertains to the use of nonsteroidal anti-inflammatory compounds for the manufacture of medicinal agents for the treatment of inflammation, other selected compounds, and the methods of production of these compounds.

In addition to a large number of steroidal compounds that bind well to the glucocorticoid receptor and act as anti-inflammatory agents (glucocorticoids), nonsteroidal compounds also are known that, even though they bind to the glucocorticoid receptor, so far have not been shown to have anti-inflammatory effects [cf. Nature Medicine **4** (1998) 92, Mol. Pharmacol. **52** (1997) 571]. In addition, nonsteroidal compounds have been described that are derived from steroidal compounds, have affinity for the glucocorticoid receptor, and probably have receptor-mediated anti-inflammatory effects [J. Med. Chem. **36** (1993), 3278-3285]. In animal experiments, however, these compounds have shown no advantages over steroidal glucocorticoids; i.e., it was not possible to separate their anti-inflammatory activity from metabolic effects, such as suppression of adrenal function.

Nonsteroidal compounds are known from WO 98/54159 that have high gestagenic activity. The document notes that some of the claimed compounds also act at the glucocorticoid and/or the mineralocorticoid receptor. However, concrete compounds are not named, nor are test results disclosed. That means that no specific compounds from the pool of generic compounds claimed in WO 98/54159 are known that have both high gestagenic activity and also act at the glucocorticoid receptor. From the standpoint of a commercial application, however, it would be advantageous to have compounds that are selective with regard to the activities mentioned.

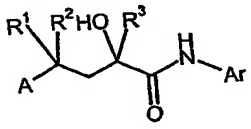
Known from WO 00/32584, furthermore, are nonsteroidal anti-inflammatory phenol derivatives that exhibit an activity dissociation between anti-inflammatory effects and the undesired metabolic side effects.

With regard to their activity dissociation between anti-inflammatory effects and the undesired metabolic side effects, the state-of-the-art compounds that have been disclosed are in need of improvement.

The task presented itself, therefore, to make available new nonsteroidal anti-inflammatory agents whose activity dissociation was as good as or better than that of the state-of-the-art compounds.

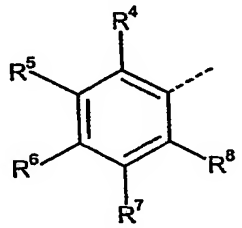
Nonsteroidal compounds have now been found that bind well to the glucocorticoid receptor and that, mediated by this binding, exercise an anti-inflammatory effect. In experiments, these compounds have shown an activity dissociation between anti-inflammatory effects and undesired metabolic side effects that is markedly better or at least as good as that of the previously described nonsteroidal glucocorticoids. The efficacy of these new compounds, therefore, is superior to or at least as good as that of the older compounds.

Pursuant to the present invention, the following compounds with general formula I are suitable for use in the manufacture of medicinal agents that possess an anti-inflammatory effect,



(I)

where R^1 and R^2 are alike or different and stand for a hydrogen atom, a C_1-C_5 alkyl group or, together with the C atom of the chain, for a ring with a total of three to seven members, and R^3 stands for a straight-chained or branched C_1-C_5 alkyl group or a straight-chained or branched, partially or completely fluorinated C_1-C_5 alkyl group. A stands for the following group (the dashed line indicates the point of attachment),

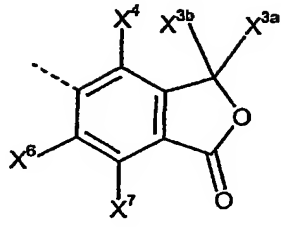


where R^4 to R^8 are the same or different and stand for a hydrogen atom, a halogen atom, a cyano group, a nitro group, or $COOR^9$ group, where R^9 stands for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group or a benzyl group, a $CONR^{10}$ group, where R^{10} stands for a hydrogen atom or a straight-chained or branched C_1-C_5 alkyl group, an NHR^{11} group, where R^{11} can stand for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched, partially or completely fluorinated C_1-C_5 alkyl group, a C_1-C_5 acyl group, an $SO_2(C_1$-$C_5)$ alkyl group or an SO_2-phenyl group that likewise has been substituted by a halogen or a C_1-C_5 alkyl group.

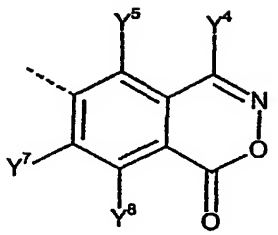
R^4 to R^8 can also stand for a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched C_2-C_5 alkenyl group, a straight-chained or branched C_2-C_5 alkinyl group, straight-chained or branched C_1-C_5 alkyl group that has been partially or completely substituted by fluorine atoms, a C_1-C_5 acyl group, an aryl residue, or a heteroaryl residue.

R^4 and R^5, together with the two carbon atoms of the A ring, stand for a saturated or unsaturated carbocyclic ring with a total of five to seven members.

Ar stands for a ring system selected from the group with general formula 1 or 2



1



2

where the residues X^{3a}, X^{3b}, X^4, X^6, X^7 (in partial formula 1) and Y^4, Y^5, Y^7, Y^8 (in partial formula 2) are the same or different and stand for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched partially or fluorinated C_1-C_5 alkyl group.

The residues X^4, X^6, X^7 (in partial formula 1) and Y^5, Y^7, Y^8 (in partial formula 2), furthermore, are the same or different and stand for a hydrogen atom, a halogen atom, a hydroxy group, a C_1-C_5 alkoxy group, or a C_1-C_5 alkanoyloxy group. They also can stand for their racemates, their separately occurring stereoisomers, and their physiologically tolerable salts.

The compounds pursuant to the invention with general formula I can occur with asymmetry centers in the form of different stereoisomers. Both the racemates and the separately occurring stereoisomers are part of the present invention.

Part of the present invention in particular are the isomers that rotate the plane of polarized light in such a way that they are designated (+)- compounds.

The substituents defined as groups or residues in the compounds with general formula I can also have the following meanings.

The C_1-C_5 alkyl groups R^1, R^2, R^3, R^4, R^5, R^{12}, X^n, Y^o can be straight-chained or branched and can stand for methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-2-dimethylpropyl, 2-methylbutyl, or 3-methylbutyl groups. A methyl or ethyl group is preferred.

When R^1 and R^2, together with the C atom of the chain, form a ring with three to seven members, this, too, can be substituted by one or two oxygen atoms and be, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring.

For a partially or completely fluorinated C_1-C_5 alkyl group, the partially or completely fluorinated alkyl groups mentioned above can be considered. Preferred among them are the trifluoromethyl or pentafluoroethyl groups, as well as the partially fluorinated alkyl groups, such as the 5,5,5,4,4-pentafluoropentyl or 5,5,5,4,4,3,3-heptafluoropentyl group. The trifluoromethyl group and the pentafluoroethyl group are preferred.

The substituents on phenyl ring A can, independent of one another, have the meanings given in the claims, namely, a hydrogen atom, a halogen atom, a cyano group, a nitro group, or an NHR^{11} group, where R^{11} can stand for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched, partially or completely fluorinated C_1-C_5 alkyl group, a C_1-C_5 acyl group, an $SO_2(C_1$-$C_5)$ alkyl group or an SO_2-phenyl group that likewise has been substituted by a halogen or a C_1-C_5 alkyl group. They can also stand for a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched C_2-C_5 alkenyl group, a straight-chained or branched C_2-C_5 alkinyl group, straight-chained or branched C_1-C_5 alkyl group that has been partially or completely substituted by fluorine atoms, a C_1-C_5 acyl group, an aryl residue, or a heteroaryl residue.

In addition, R^4 and R^5, together with the two carbon atoms of the A ring, can stand for a saturated or unsaturated carbocyclic ring with a total of five to seven members, such as indan, naphthalene, tetrahydronaphthalene, and benzocycloheptane.

An integral part of the invention is the use of the compounds with general formula I, where R^4 to R^8 are the same or different and stand for a hydrogen atom, a halogen atom, a cyano group, a nitro group, a $COOR^9$ group, where R^9 stands for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group or a benzyl group, a $CONR^{10}$ group, where R^{10} stands for a hydrogen atom or a straight-chained or branched C_1-C_5 alkyl group, an NH^{11} group, where R^{11} can stand for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched, partially or completely fluorinated C_1-C_5 alkyl group, a C_1-C_5 acyl group, an SO_2(C_1-C_5) alkyl group or an SO_2-phenyl group that likewise has been substituted by a halogen or a C_1-C_5 alkyl group. R^4 to R^8 can also stand for a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched C_2-C_5 alkenyl group, a straight-chained or branched C_2-C_5 alkinyl group, a straight-chained or branched C_1-C_5 alkyl group that has been partially or completely substituted by fluorine atoms, a C_1-C_5 acyl group, an aryl residue, or a heteroaryl residue.

The terms halogen atom and halogen refer to a fluorine, chlorine, bromine, or iodine atom. Fluorine, chlorine, and bromine atoms are preferred.

For the C_2-C_5 alkenyl group, a vinyl, 2-substituted vinyl, 1-propenyl, 2-propenyl, 2- or 3-substituted propenyl, 1-butenyl, 2-butenyl, 3- butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, and 3-methyl -

1-butenyl can be considered. The alkenyl groups that have the double bond in the 1 or 2 position are preferred. As substituents for the vinyl group or the propenyl group, the methyl group or the ethyl group should receive primary consideration.

The C_2-C_5 alkinyl group can be, for example, an ethinyl, 1-propinyl, 2-propinyl, 2-butinyl, 3-methyl-1-butinyl, 4-methyl-1-butinyl, or 1-pentinyl group. The alknyl groups that have a triple bond in the 1 or 2 position are preferred.

The C_1-C_5 acyl group can be a formyl, acetyl, propionyl, n-butyroyl, 2-methylpropionyl, n-valeroyl, 2-methylbutyroyl, 3-methylbutyroyl, or pivaloyl group.

The sulfonyl(C_1-C_5) alkyl group R^{11} can be, for example, a methylsulfonyl or an ethylsulfonyl group.

The halogen- or C_1-C_5 alkyl group-substituted sulfonylphenyl group R^{11} can be 2-chloro(phenylsulfonyl), 3-chloro(phenylsulfonyl), 4-chloro(phenylsulfonyl), 2-methyl(phenylsulfonyl), 3-methyl(phenylsulfonyl), or 4-methyl(phenylsulfonyl). The sulfonyl group is bound by its valence electrons to the hydrogen atom of the NHR^{11} group.

Aryl means a phenyl group or a substituted phenyl group.

Substituents that can be considered for the aryl group are halogen atoms, the cyano, nitro, C_1-C_5 alkoxy, amino, hydroxy, carboxy, and C_1-C_5 alkanoyl groups, branched or unbranched C_1-C_5 alkyl groups, and branched or unbranched C_1-C_5 alkyl groups that are partially or completely fluorinated.

The heteroaryls include aromatic heterocyclic five- and six-member ring structures that can contain other heteroatoms, such as oxygen, hydrogen, or sulfur. Heterocyclic five-member ring structures are preferred, especially the furyl, thienyl, pyridyl, thiazolyl, oxazolyl, oxadiazolyl, and imidazolyl radicals.

The heteroaryl groups can be substituted by branched and unbranched C_1-C_5 alkyl groups, branched and unbranched C_1-C_5 alkyl groups that can be fluorinated, and/or halogen atoms.

The hydroxy groups that can represent the X^n, Y^o residues can be either ethers or esters, as follows:
The above-mentioned alkyl groups, especially the methyl or ethyl groups, can be considered as the C_1-C_5 alkyl group to be used for the etherization of hydroxy groups.

Formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, and pivaloyl groups can be considered as the C_1-C_5 alkanoyl group to be used in the esterification of hydroxy groups. The acetyl group is preferred.

Examples of possible C_1-C_5 acyl groups for the esterification of hydroxy groups include the above-mentioned alkanoyl groups, preferably again an acetyl group or a benzoyl, toluoyl, phenylacetyl, acryloyl, cinnamoyl or cyclohexylcarbonyl group.

A formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, or isovaleryloxy group can be considered as the C_1-C_5 alkanoyloxy group for X^4, X^6, X^7, Y^4, Y^5, Y^7, or Y^8.

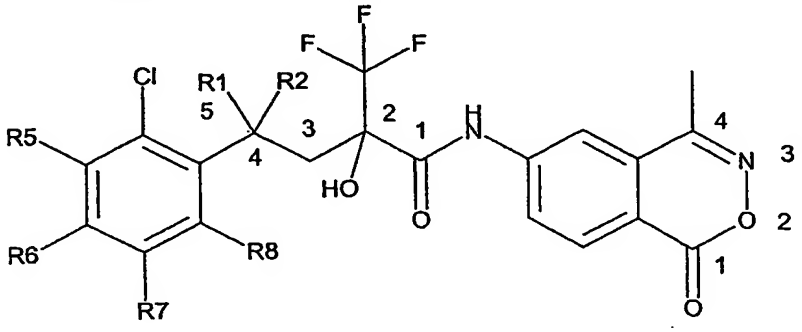
Preferred are compounds in which Ar stands for partial formula 2 and Y^4 stands for a methyl group.

Particularly preferred are compounds in which Ar stands for partial formula 2, Y^4 stands for a methyl group, and the other substituents Y^5, Y^7, and Y^8 are hydrogen atoms.

Nonsteroidal compounds with a mixed profile of gestagenic and androgenic activities of various strengths have already been described in WO 98/5419. The compounds with general formula I to be used pursuant to claim 1 of the present patent for the manufacture of medicinal agents with anti-inflammatory activity fall within the scope of the general formula given in WO 98/54159 but are not presented there as a preferred group or directly disclosed as compounds. Thus, because of their anti-inflammatory activity that is dissociated from undesired metabolic or other effects, they are new and also meet the patent requirements for inventive activity.

Undesired activities/effects in the sense of the present invention are metabolic effects or binding to other steroid receptors.

The compounds with general formula I named below fall within the scope of the general formula given in WO 98/54159 but are not mentioned there by name. Thus, because of their anti-inflammatory activity that is dissociated from undesired metabolic or other effects, they are new and also meet the patent requirements for inventive activity. The compounds listed below, therefore, are part of the present invention. The following example is intended to elucidate these compounds:



6-[4-(2-Chlor-3-R^5-4-R^6-5-R^7-6-R^8-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

The following compounds are the subject of the present invention.

5-[4-(5-Fluor-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-phthalid

6-[4-(2-Chlor-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(5-Fluor-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-phthalid

6-[4-(5-Fluor-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(3-Fluor-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-phthalid

6-[4-(3-Fluor-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on 6-[4-(5-Fluor-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(5-Fluor-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(5-Fluor-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(4-trifluormethylphenyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(4-trifluormethylphenyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(4-trifluormethylphenyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(3,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(3,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(3,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Cyano-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Ethenyl-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Ethyl-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Fluor-2-phenylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Fluor-2-(furan-2'-yl)phenyl}-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-3-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-3-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-3-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-4-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-4-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-4-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-6-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-6-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-6-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,4-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,4-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,4-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,5-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,5-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,5-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(4-Brom-2-chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(4-Brom-2-chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(4-Brom-2-chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylhexanoylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylhexanoylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,4-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,4-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,4-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3,5-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3,5-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3,5-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3,4-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3,4-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3,4-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(3-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(3-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(3-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(4-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(4-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(4-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Fluor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Fluor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Fluor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Bromphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Bromphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Bromphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(4-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(4-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(4-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(5-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(5-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Chlor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(5-Chlor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(5-Chlor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-) 6-[3-{1-(2-Chlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+) 6-[3-{1-(2-Chlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,4-Dichlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,4-Dichlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,4-Dichlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,4-Dichlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,4-Dichlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,4-Dichlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Trifluormethyl-phenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-) 6-[3-{1-(2-Trifluormethyl-phenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+) 6-[3-{1-(2-Trifluormethyl-phenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,3-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,3-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3-Difluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[3-{1-(2,3-Difluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[3-{1-(2,3-Difluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,5-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,5-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,5-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3,5-Trifluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3,5-Trifluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Bromphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Bromphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Bromphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-phthalid

(-) 5-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-phthalid

(+) 5-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-phthalid

6-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4- methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4- methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4- methyl-2,3-benzoxazin-1-on

6-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4- methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4- methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4- methyl-2,3-benzoxazin-1-on

5-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(-) 5-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(+) 5-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

5-[4-(5-Fluor-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(-) 5-[4-(5-Fluor-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(+) 5-[4-(5-Fluor-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

6-[4-(2-Brom-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Brom-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Brom-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-4-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-4-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-4-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on

6-{3-[4-(2-Chlor-5-fluorphenyl)-tetrahydropyran-4-yl]-2-hydroxy-2-trifluormethylpropionylamino}-4-methyl-2,3-benzoxazin-1-on

(-) 6-{3-[4-(2-Chlor-5-fluorphenyl)-tetrahydropyran-4-yl]-2-hydroxy-2-trifluormethylpropionylamino}-4-methyl-2,3-benzoxazin-1-on

(+) 6-{3-[4-(2-Chlor-5-fluorphenyl)-tetrahydropyran-4-yl]-2-hydroxy-2-trifluormethylpropionylamino}-4-methyl-2,3-benzoxazin-1-on

A special aspect of the present invention is the above-named 2,3-benzoxazine-1-ones.

Another aspect of the present invention is the above-named compounds whose 2,3-benzoxazine-1-one has a methyl group in its 3 position.

Compounds with general formula I can occur in the form of salts, including, for example, the hydrochloride, sulfate, nitrate, phosphate, pivalate, maleate, fumarate, tartrate, benzoate, mesylate, citrate, or succinate.

When the compounds according to the invention are racemic

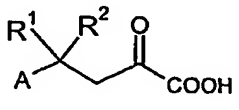
mixtures, they can be separated by the usual methods known to the professional into pure optically active forms. For example, racemic mixtures can be separated into their pure isomers by chromatography in a carrier material that itself is optically active (e.g., CHIRALPAK AD®). It is also possible to esterify the hydroxy group in a racemic compound with general formula I with an optically active acid and to separate the diastereoisomeric ester by fractionated crystallization or chromatography and to saponify the separated ester to the optically pure isomeric form. Examples of optically active acids that can be used are mandelic acid, camphor sulfonic acid, and tartaric acid.

Methods for the Production of the Compounds Pursuant to the Invention

The compounds pursuant to the invention can be obtained by starting with a commercially available phenyl compound or a phenyl compound that can be produced by known methods and from this compound forming the chain $C(R^1)(R^2)-CH_2-C(OH)(R^3)-B-NH-Ar$. In the final step, the R^3 residue is introduced or the ring system of formula 1 or formula 2 (=Ar) is introduced by the formation of the amide compound B-NH-Ar.

If desired, compounds that have been produced by one of the following methods and in which A is a substituted aromatic ring can be selectively substituted at this aromatic ring according to known methods. Examples of this method are the catalytic hydration of multiple bonds, nitrogenization, and halogenization. Halogen and nitrogen substitution, moreover, offer the possibility of further modifications. For example, aryl bromides can be reacted with boron, tin, or zinc reagents with palladium catalysis by the usual methods known to the professional. Nitro compounds can be reduced to aniline derivatives hydrogenolytically or with metals, such as iron or zinc. After diazotization, the aniline derivatives can be further reacted--in the Sandmeyer reaction, for example.

(A)
An alpha-ketocarbonic acid with general formula II



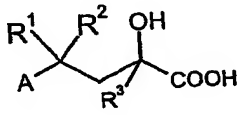
(II)

where A, R^1, and R^2 have the meanings given for formula I, is

either esterified or is reacted with a compound with general formula III

$$(R^{12})_3SiR^3 \qquad (III)$$

where R^3 has the meaning given for general formula I and R^{12} stands for a C_1-C_5 alkyl group, to form a compound with general formula IV. The reaction takes place in the presence of a catalyst or with an alkyl metal compound, such as the Grignard reagent or a lithium alkyl.



(IV)

Fluoride salts or basic compounds such as alkali carbonates [J. Am. Chem. Soc. 111, 393 (1989)] can be considered for use as the catalysts. If desired, the ester can be cleaved again and then reacted with a compound with general formula V

$$Ar\text{-}NH\text{-}R^{13} \qquad (V)$$

where R^{13} is a hydrogen atom or a C_1-C_5 acyl group and Ar has the meaning given for general formula I. Subsequently, the R^{13} residue is split off in order to obtain a compound with formula I or reacted directly with a compound with general formula V

$$Ar\text{-}NH\text{-}R^{13} \qquad (V)$$

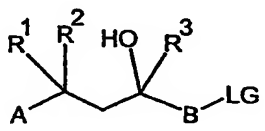
where R^{13} is a hydrogen atom or a C_1-C_5 acyl group and Ar has the meaning given for general formula I, possibly after activation of the acid function by, for example, transformation to the acid

chloride. Subsequently, in the desired sequence, the R^{13} residue is split off and the compound is reacted with a compound with general formula III

$$(R^{12})_3SiR^3 \qquad (III)$$

where R^3 and R^{12} have the meanings given above, in order to obtain a compound with general formula I

(B)
A compound with general formula VI



(VI)

where A, B, R^1, R^2, and R^3 have the meanings given for formula I and LG is any desired volatile group, is reacted with a compound with general formula V

$$Ar\text{-}NH\text{-}R^{13} \qquad (V)$$

where R^{13} is a hydrogen atom or a C_1-C_5 acyl group and Ar has the meaning given for general formula I. Subsequently, the R^{13} residue is split off in order to obtain a compound with general formula I.

The compound with general formula VI can be only an intermediate product that, if desired, can be isolated or simply produced in situ. It can be, for example, an intermediate formed from an acid chloride that was formed from the corresponding carbonic acid. The volatile group can be, for example, a fluorine,

chlorine, or bromine atom, or when no intermediate acid chloride is formed, it can be the mesylate or tosylate residue.

The binding of the substances to the glucocorticoid receptor (GR) is determined using a receptor that is manufactured by recombination. Cytosol preparations of Sf9 cells that have been infected with recombinant baculovirus that codes for the GR are used in the binding studies. Compared with the reference substance, [^{3}H]dexamethasone, the substances show a great to very great affinity for the GR.

In addition, these compounds show affinity for the mineralocorticoid receptor (MR) in the MR binding test that uses cytosol preparations of Sf9 cells that have been infected with recombinant baculovirus that codes for the MR and [^{3}H]aldosterone as the reference substance.

The essential molecular mechanism for the anti-inflammatory effect of glucocorticoids is thought to be the GR-mediated inhibition of the transcription of cytokines, adhesion molecules, enzymes, and other pro-inflammatory factors. This inhibition is due to an interaction of the GR with other transcription factors, such as AP-1 and NF-kappa-B (for an overview, see Cato, ACB, and Wade, E. BioEssays **18**, 371-378, 1996).

The compounds pursuant to the invention with general formula I inhibit lipopolysaccharide (LPS)-induced secretion of cytokine IL-8 in the human THP-a monocyte cell line. The concentrations of the cytokines was determined in the supernatant by means of commercially available ELISA kits.

The anti-inflammatory activity of the compounds with general formula I was tested on croton oil-induced inflammation in rats

and mice [J. Exp. Med. (1995), **182**, 99-108]. In these experiments, the croton oil was applied topically in ethanolic solution to the ears of the animals. The test compounds were administered topically or systemically at the same time as or 2 hours before the croton oil. After 16-24 hours, the weight of the ears was used as the measure of inflammatory edema, peroxidase activity was used as the measure of granulocyte infiltration, and elastase activity was used as the measure for the infiltration of neutrophilic granulocytes. In this test, the compounds with general formula I inhibited these three inflammatory parameters after both topical and systemic administration.

One of the most frequent undesired side effects of glucocorticoid therapy is so-called steroid diabetes [cf. Hatz, HJ, Glucocorticoids: immunologic basis, pharmacology, and therapeutic guidelines. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1998]. This is caused by the stimulation of gluconeogenesis in the liver by induction of the responsible enzymes and by free amino acids that occur with the breakdown of proteins (catabolic effect of glucocorticoids). A key enzyme in the catabolic metabolism of the liver is tyrosine amino transferase (TAT). The activity of this enzyme can be determined photometrically from liver homogenates and is a good measure of the undesired metabolic effects of the glucocorticoids. To measure TAT induction, the animals were killed 8 hours after administration of the test compounds, their livers were removed, and the TAT activity in the homogenate was measured. In this test, anti-inflammatory doses of the compounds with general formula I induced the TAT only slightly or not at all.

In summary, the new compounds with general formula I exhibit the following properties that differentiate them from previously used

steroidal glucocorticoids:

- Nonsteroidal structure (i.e., the substances are effective in patients who cannot use traditional glucocorticoids because they are allergic to the basic structures of the steroids [cf. Lutz, ME, el-Azhary, RA, Mayo Clin. Proc. **72**, 1141-1144, 1997])
- Similar anti-inflammatory effect with only slight metabolic activity

Because of their anti-inflammatory and additional anti-allergic, immunosuppressive, and antiproliferative activity, the compounds with general formula I pursuant to the invention can be used as medications for the treatment or prophylaxis of the following disease states in mammals and humans: In this context, the term "disease" stands for the following indications:

(i) Pulmonary diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
   - Chronic obstructive pulmonary diseases of all etiologies, bronchial asthma in particular
   - Bronchitis of various etiologies
   - All forms of restrictive pulmonary disease, allergic alveolitis in particular
   - All forms of pulmonary edema, toxic pulmonary edema in particular
   - Sarcoidosis and granulomatosis, especially Boeck's disease

(ii) Rheumatic diseases, autoimmune diseases, and diseases of the joints that are accompanied by inflammatory, allergic, and/or proliferative processes:
   - All forms of rheumatic disease, rheumatoid arthritis, acute rheumatic fever, and polymyalgia rheumatica in particular

- Reactive arthritis
- Inflammatory soft tissue diseases of other etiologies
- Arthritic symptoms in patients with degenerative joint diseases (arthroses)
- Traumatic arthritides
- Collagenoses of every etiology, e.g., systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, Sjögren's syndrome, Still's syndrome, Felty's syndrome

(iii) Allergies that are accompanied by inflammatory, allergic, and/or proliferative processes:
- All forms of allergic reaction, e.g., Quincke's edema, hay fever, insect bites, allergic reactions to medications, blood derivatives, contrast media, etc., anaphylactic shock, urticaria, contact dermatitis

(iv) Vascular inflammation (vasculitides)
- Panarteritis nodosa, arteritis temporalis, erythema nodosum

(v) Dermatologic diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Atopic dermatitis (especially in children)
- Psoriasis
- Pityriasis rubra pilaris
- Erythematous diseases caused by various noxae, e.g., radiation, chemicals, burns
- Bullous dermatoses
- Lichenoid diseases
- Pruritus (e.g., those of allergic etiology)
- Seborrheic exanthema
- Rosacea
- Pemphigus vulgaris
- Erythema multiforme exsudativum
- Balanitis

- Vulvitis
- Hair loss, such as alopecia areata
- Cutaneous T cell lymphoma

(vi) Kidney diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Nephrototic syndrome
- All nephritides

(vii) Liver diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Acute hepatic cell degeneration
- Acute hepatitis of various etiologies, e.g., viral, toxic, drug induced
- Chronic aggressive and/or chronic intermittent hepatitis

(viii) Gastrointestinal diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Regional enteritis (Crohn's disease)
- Ulcerative colitis
- Gastritis
- Reflux esophagitis
- Gastroenteritides of other etiologies, e.g., endemic sprue

(ix) Proctologic diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Anal eczema
- Fissures
- Hemorrhoids
- Idiopathic proctitis

(x) Eye diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Allergic keratitis, uveitis, iritis
- Conjunctivitis
- Blepharitis

- Neuritis nervi optici
- Chorioiditis
- Sympathic ophthalmia

(xi) Ear, nose, and throat diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Allergic rhinitis, hay fever
- Otitis externa, e.g., that caused by contact eczema, infection, etc.
- Otitis media

(xii) Neurologic diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Brain edema, especially that caused by a tumor
- Multiple sclerosis
- Acute encephalomyelitis
- Meningitis
- Various forms of convulsions, e.g., BNS seizures

(xiii) Blood diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Acquired hemolytic anemia
- Idiopathic thrombocytopenia

(xiv) Neoplastic diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Acute lymphatic leukemia
- Malignant lymphoma
- Lymphogranulomatoses
- Extensive metastasis, especially in the case of breast, bronchial, or prostate carcinoma

(xv) Endocrine diseases that are accompanied by inflammatory, allergic, and/or proliferative processes:
- Endocrine orbitopathy
- Thyrotoxic crisis
- de Quervain's thyroiditis
- Hashimoto's thyroiditis

- Basedow's disease

(xvi) Organ and tissue transplantation, graft-versus-host disease

(xvii) Severe shock conditions, e.g., anaphylactic shock, systemic inflammatory response syndrome (SIRS)

(xviii) Substitution therapy in patients with
- Congenital primary adrenal insufficiency, e.g., congenital adrenogenital syndrome
- Acquired primary adrenal insufficiency, e.g., Addison's disease, autoimmune adrenalitis, postinfectious, tumors, metastases, etc.
- Congenital secondary adrenal insufficiency, e.g., congenital hypopituitarism
- Acquired secondary adrenal insufficiency, e.g., postinfectious, tumors, etc.

(xix) Emesis that is accompanied by inflammatory, allergic, and/or proliferative processes:
- e.g., in combination with 5-HT_3 antagonist in cytostatic-induced emesis

(xx) Pain of inflammatory etiology, e.g., lumbago

In addition, the compounds pursuant to the invention with general formula I can be used for the treatment and prophylaxis of other disease states not named above for which synthetic glucocorticoids currently are employed [see Hatz, HJ, Glucocorticoids: immunologic basis, pharmacology, and therapeutic guidelines. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1998].

All of the above-named indications (i-xx) are thoroughly described in Hatz, HJ, Glucocorticoids: immunologic basis, pharmacology, and therapeutic guidelines. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1998.

The appropriate therapeutic dose for the disease states named above varies and depends, for example, on the strength of the compound with general formula I, the host, the route of administration, and the nature and severity of the condition to be treated. The appropriate dose also depends on whether the compound is used prophylactically or therapeutically.

The invention also provides

(i) The use of one of the compounds pursuant to the invention with formula I or a mixture of these compounds for the manufacture of a medication for the treatment of a DISEASE;

(ii) A method for the treatment of a DISEASE that includes administration of an amount of the compound pursuant to the invention that suppresses the disease and in which the amount of the compound is given to a patient who needs such a medication;

(iii) A pharmaceutical preparation for the treatment of a DISEASE whose treatment includes one of the compounds pursuant to the invention or a mixture of these compounds and that includes at least one pharmaceutical aid and/or carrier substance.

Generally, in the case of animals, satisfactory results can be expected when the daily dose of the compound pursuant to the invention ranges from 1 to 100,000 μg per kilogram of body weight. In the case of larger mammals, humans, for example, the recommended daily dose ranges from 1 to 100,000 μg per kilogram of body weight. A dose of 10 to 30,000 μg per kilogram of body weight is preferred. More preferred is a dose of 10 to 10,000 μg per kilogram of body weight. It is advantageous, for example, to administer this dose several times a day. For the treatment of acute shock (e.g., anaphylactic shock), individual doses can be

given that are markedly higher than the doses described above.

The pharmaceutical preparations based on the new compounds are formulated in the usual way by combining the active substance with the usual carriers, fillers, disintegration aids, binders, wetting agents, lubricants, absorption enhancers, diluents, taste enhancers, pigments, etc., and then processing them to the desired dosage form. The reader is referred to Remington's Pharmaceutical Science, 15th Ed., Mack Publishing Co., Easton, Pennsylvania (1980).

For oral administration, tablets, coated tablets, capsules, pills, powders, granules, pastilles, suspensions, emulsions, and solutions can be considered in particular.

For parenteral administration, injection and infusion preparations are possible.

Appropriately prepared crystal suspensions can be used for intra-articular injection.

For intramuscular injection, aqueous and oily injection solutions or suspensions and appropriate depot preparations can be used.

For rectal administration (systemic or local), the new compounds can be used in the form of suppositories, capsules, solutions (e.g., in the form of enemas), and salves.

For pulmonary administration, the new compounds can be used in the form of aerosols and other inhaled preparations.

For topical administration, formulations such as gels, salves, ointments, cremes, pastes, powders, milks, and tinctures are

possible. To allow a satisfactory pharmacologic effect to be achieved, the dose of the compounds with general formula I in such preparations should be 0.01% to 20%.

The invention also includes the compounds pursuant to the invention with general formula I as therapeutic active ingredients. In addition, the invention includes the compounds pursuant to the invention with general formula I as therapeutic active ingredients together with pharmaceutically tolerable and acceptable aids and carriers. The invention likewise includes a pharmaceutical formulation that contains one of the pharmaceutically active compounds pursuant to the invention or a mixture of these compounds and a pharmaceutically tolerable salt or pharmaceutically tolerable aid or carrier.

The following examples serve to further explain the invention but the invention is not restricted to them. The synthesis of important precursors that are not disclosed in the Experimental Section are already known and can be found, for example in WO 98/54159.

Experimental Section

Example 1

6-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

Example 2

5-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide

Precursors:

2-(5-Fluoro-2-methylphenyl)-2-methylpropionitrile
5.25 g of (5-Fluoro-2-methylphenyl)acetonitrile and 5.25 ml of methyl iodide are dissolved in 70 ml of dimethylformamide and mixed over 2.5 h with ice cooling with 2.7 g of sodium hydride (80%). After 3 h at 0°C and 16 h at room temperature, ice water and ethyl acetate are added, the mixture is rendered acid with 1 M hydrochloric acid, and the ethyl acetate phase is washed with water, dried (Na_2SO_4), and evaporated. The yield is 6.1 g of 2-(5-fluoro-2-methylphenyl)-2-methylpropionitrile in the form of an oil.

2-(5-Fluoro-2-methylphenyl)-2-methylpropionaldehyde
6.1 g of 2-(5-fluoro-2-methylphenyl)-2-methylpropionitrile dissolved in 60 ml of toluene is mixed over 45 min at -70°C with 44 ml of 1.2 M diisobutyl aluminum hydride solution in toluene. After 4 h at -78°C, 120 ml of ethyl acetate is added dropwise. The mixture is warmed to room temperature and washed twice with 2 N sulfuric acid and once with water. The ethyl acetate phase is dried (Na_2SO_4) and evaporated. After distillation, the yield is 5.3 g of 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde; boiling point 120°/0.031 hPa.

4-(5-Fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid
A solution of 8.04 ml of 2-diethylphosphono-2-ethoxy acetic acid ethyl ester is 40 ml of tetrahydrofuran is mixed with ice cooling over 20 minutes with 16.5 ml of a 2 M solution of lithium diisopropylamide in tetrahydrofuran/heptane/toluene and stirred for 30 min at 0°C. Over 30 min, a solution of 5.2 g of 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde in 30 ml of tetrahydrofuran is added dropwise at 0°C. After 20 h at room temperature, 2 N sulfuric acid is added, and the mixture is extracted with ethyl acetate, dried (Na_2SO_4), and evaporated. The raw product is saponified with 100 ml of 2 M sodium hydroxide

solution. The yield is 5 g of acid, which then is heated with 450 ml of 2 N sulfuric acid with vigorous stirring and refluxing for several hours. After extraction with ethyl acetate and washing with water, 4 g of 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid is obtained in the form of a yellowish oil.

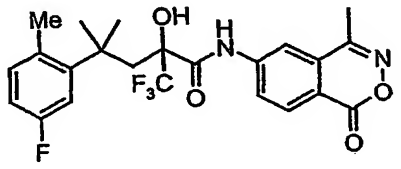
5-[4-(5-Fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino] phthalide

950 mg of 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid in 15 ml of dimethylacetamide is mixed at -10°C with 0.322 ml of thionyl chloride, stirred for 30 min at -10° and for 1 h at 0°C, and combined with 750 mg of 5-aminophthalide. After 16 h at room temperature, the combination is mixed with 2 M hydrochloric acid and ethyl acetate, and the organic phase is washed to neutrality with water, dried (Na_2SO_4), and evaporated. After chromatography on kieselgel with hexane/ethyl acetate (3:2) and recrystallization from diisopropyl ether, 486 mg of 5-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino] phthalide is obtained; freezing point 153°C.

6-[4-(5-Fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one

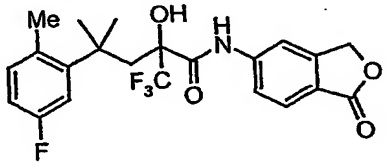
Obtained in a manner analogous to that of 5-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino] phthalide using 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid and 6-amino-2,3-benzoxazine-1-one; freezing point 186°C.

6-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



514 mg of 6-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one in 10 ml of dimethylformamide is combined at 0°C with 192 mg of cesium carbonate and 0.44 ml of trifluoromethyl(trimethyl)silane. After 1 h at 0°C and 16 h at room temperature, the mixture is cooled again to 0°C and mixed with 1.3 ml of a 1 M tetrabutyl ammonium fluoride solution in tetrahydrofuran. After 30 min at 0°C, 2 N sulfuric acid and ethyl acid are added, and the ethyl acetate phase is washed with water, dried (Na_2SO_4), and evaporated. After chromatography on kieselgel with hexane/ethyl acetate (3:2), 220 mg of 6-[4-(5-fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one is obtained; freezing point 175-176°C.

6-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide



Obtained in a manner analogous to Example 1 from 5-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino] phthalide; freezing point 165-168°C.

Separation of the enantiomers from Example 1:

The enantiomer mixture from Example 1 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (9:1, vol/vol). In this way, the following are obtained from 140 mg of racemate:

(-) 6-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the first fraction: 57 mg [freezing point 203-204°C; $alpha_D$ = -92.7° (c = 0.5 in tetrahydrofuran)] and

(+) 6-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the second fraction: 56 mg [freezing point 202-203°C]

Example 3

6-[4-(2-Chloro-5-fluorolphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

Precursors:

2-(5-Chloro-5-fluorophenyl)-2-methylpropionitrile

2-(5-Chloro-5-fluorophenyl)-2-methylpropionitrile is synthesized in a manner analogous to that described for; boiling point 100°C/0.04 hPa.

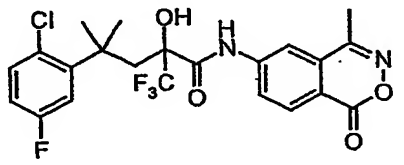
2-(2-Chloro-5-fluorophenyl)-2-methylpropionaldehyde

2-(2-Chloro-5-fluorophenyl)-2-methylpropionaldehyde is obtained in a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde; boiling point 120°C/0.04 hPa.

4-(2-Chloro-5-fluorophenyl)-4-methyl-2-oxovaleric acid
4-(2-Chloro-5-fluorophenyl)-4-methyl-2-oxovaleric acid is obtained as an oil in a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid.

6-[4-(2-Chloro-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one
Obtained in a manner similar to that described for 5-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino] phthalide from 4-(2-chloro-5-fluorophenyl)-4-methyl-2-oxovaleric acid and 6-amino-2,3-benzoxazine-1-one; freezing point 198-199°C.

6-[4-(2-Chloro-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



is obtained in a manner analogous to that described for Example 1 from 6-[4-(2-chloro-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-2,3-benzoxazine-1-one; freezing point 201-203°C.

<u>Separation of the enantiomers from Example 3:</u>

The enantiomer mixture from Example 3 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (9:1, vol/vol). In this way, the following are obtained from 190 mg of racemate:

(-) 6-[4-(2-Chloro-5-fluorolphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as

the first fraction: 61 mg [freezing point 247-249°C, $alpha_D$ = -74.2° (c = 0.5 in tetrahydrofuran)] and

(-) 6-[4-(2-Chloro-5-fluorolphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the second fraction: 74 mg [freezing point 247-249°C]

The compounds described in Tables 1-3 are obtained in a manner analogous to that described for Example 3.

Chlorine compounds:

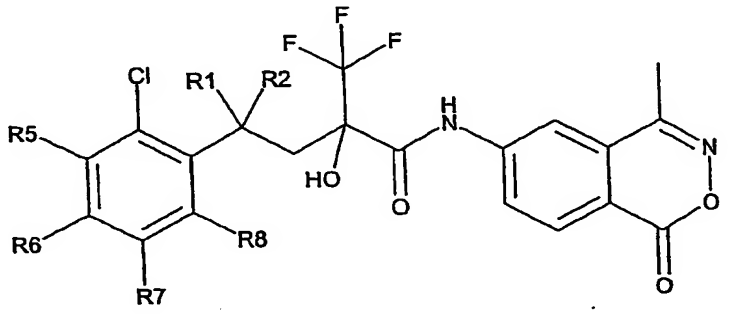


Table 1: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	R1 / R2	Fp. [°C]	Isomerie bzw $[\alpha]_D$
1	H	H	H	H	CH_3	169-171	Racemat
2	H	H	H	H	CH_3	198	-173.3
3	H	H	H	H	CH_3	199	(+)-Form
4	F	H	H	H	CH_3	189-192	Racemat
5	F	H	H	H	CH_3	189-192	-89,1
6	F	H	H	H	CH_3	220-223	+78,2
7	H	F	H	H	CH_3	208-209	Racemat
8	H	F	H	H	CH_3	179	-77,1
9	H	F	H	H	CH_3	181-182	+74,6
10	H	H	H	F	CH_3	222-224	Racemat
11	H	H	H	F	CH_3	232-235	-110,0
12	H	H	H	F	CH_3	230-233	+106,0
13	Cl	H	H	H	CH_3	228-230	Racemat
14	Cl	H	H	H	CH_3	252-254	-32,8
15	Cl	H	H	H	CH_3	255-256	+29,3
16	H	Cl	H	H	CH_3	249-253	Racemat
17	H	Cl	H	H	CH_3	253-255	-126,2
18	H	Cl	H	H	CH_3	252-256	(+)-Form
19	H	H	Cl	H	CH_3	210-211	-96,7
20	H	H	Cl	H	CH_3	208-209	100,8
21	H	Br	H	H	CH_3	155-157	Racemat
22	H	Br	H	H	CH_3	151-152	-16,6
23	H	Br	H	H	CH_3	150-155	(+)-Form
24	OH	H	H	H	CH_3	235-241	-75,3
25	OH	H	H	H	CH_3	236-240	+76,0

Fluorine compounds:

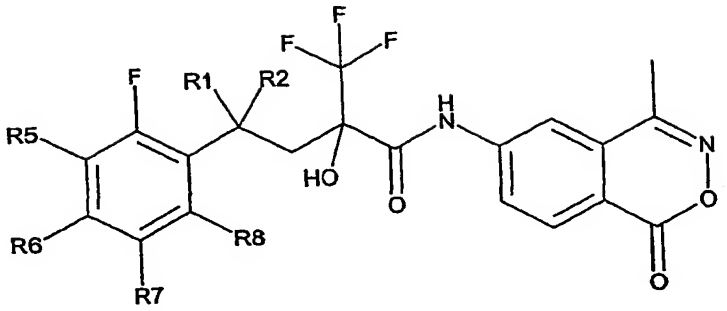


Table 2: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	R1 / R2	Fp. [°C]	Isomerie bzw $[\alpha]_D$
26	H	H	H	H	CH_3	220	-85,5
27	H	H	H	H	CH_3	227	(+)-Form
28	F	H	H	H	CH_3	204	Racemat
29	F	H	H	H	CH_3	204-205	-90,3
30	F	H	H	H	CH_3	204-205	+83.0
31	H	F	H	H	CH3	175-176	-83,8
32	H	F	H	H	CH3	176-177	(+)-Form
33	H	H	F	H	CH3	174	-81,5
34	H	H	F	H	CH3	174-176	(+)-Form
35	H	H	H	F	CH3	205-210	Racemat
36	H	H	H	F	CH3	230-240	-71,3
37	H	H	H	F	CH3	240-245	(+)-Form
38	F	H	F	H	CH3	209	Racemat
39	Cl	H	H	H	CH3	189-192	-64,0
40	Cl	H	H	H	CH3	184-187	(+)-Form
41	H	Cl	H	H	CH3	239-141	Racemat
42	H	Cl	H	H	CH3	210-215	-67,7
43	H	Cl	H	H	CH3	198-199	(+)-Form
44	OCH3	H	H	H	CH3	197-200	Racemat

Bromine compounds:

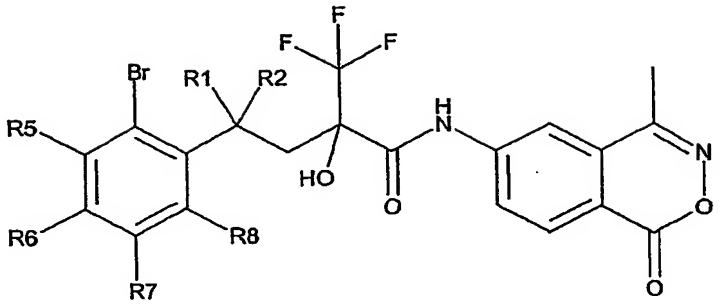


Table 3: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	R1 / R2	Fp. [°C]	Isomerie bzw $[\alpha]_D$
45	H	H	H	H	CH_3	186-191	Racemat
46	H	H	H	H	CH_3	209-211	-65,0
47	H	H	H	H	CH_3	205-207	+66,0

Example 4

5-[4-(-Fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide

Precursors

2-(3-Fluorophenyl)-2-methylpropionitrile

2-(3-Fluorophenyl)-2-methylpropionitrile is synthesized in a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionitrile; boiling point 120°C/0.04 hPa.

4-(3-Fluorophenyl)-4-methyl-2-oxovaleric acid

4-(3-Fluorophenyl)-4-methyl-2-oxovaleric acid is obtained as an oil in a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid.

4-(3-Fluorophenyl)-4-methyl-2-oxovaleric acid ethyl ester

5.6 g of 4-(3-fluorophenyl)-4-methyl-2-oxovaleric acid and 0.197 ml of sulfuric acid in 150 ml of ethanol are heated for 3 h with refluxing. The solvent is distilled off, and the residue is dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. After distillation in a bulb tube, 5.6 g of 4-(3-fluorophenyl)-4-methyl-2-oxovaleric acid ethyl ester is obtained; boiling point 130°C/0.04 hPa.

4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleric acid ethyl ester

5.3 g of 4-(3-fluorophenyl)-4-methyl-2-oxovaleric acid ethyl ester in 60 ml of dimethylformamide is combined at 0°C with 3.25 g of cesium carbonate and 4.63 ml of trifluoromethyl-(trimethyl)silane. After 1 h at 0°C and 16 h at room temperature, the mixture is cooled again to 0°C and mixed with 20 ml of a 1 M tetrabutyl ammonium fluoride solution in tetrahydrofuran. After 30 min at 0°C, 2 N sulfuric acid and ethyl acid are added, and the ethyl acetate phase is washed with water, dried (Na_2SO_4), and evaporated. After chromatography on kieselgel with hexane/ethyl acetate (20:1) and bulb tube distillation, 4.45 g of 4-(3-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleric acid ethyl ester is obtained; boiling point 100°C/0.04 hPa).

4-(5-Fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid ethyl ester

4-(3-Fluoro-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid ethyl ester

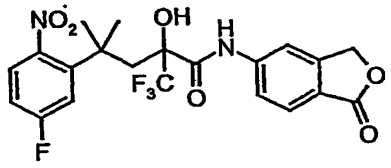
3.3 g of 4-(3-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-valeric acid ethyl ester is dissolved in 20 ml of trifluoro acetic acid and mixed at 0°C with 0.84 ml of 100% nitrous acid. After 3 h at 0°C and 16 h at room temperature, the preparation is poured onto ice, and the crystals are separated by vacuum filtration, washed with water, and dried. Recrystallization from hexane results in 2.5 g of 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid ethyl ester; freezing point 66-67°C.

Chromatography of the mother liquor on kieselgel with hexane/ethyl acetate (8:1) yields a first fraction consisting of another 500 mg of 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid ethyl ester and a second fraction consisting of 800 mg of 4-(3-fluoro-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid ethyl ester in the form of an oil.

4-(5-Fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid

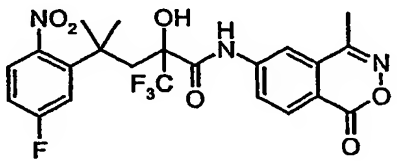
2.4 g of 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid ethyl ester is dissolved in 30 ml of ethanol and combined with 60 ml of 1 M sodium hydroxide solution. After 2 days at room temperature, the preparation is evaporated, and the residue is dissolved in water, rendered acid at 0°C, and extracted with ethyl acetate. The ethyl acetate phase is washed to neutrality with water, dried (Na_2SO_4), and evaporated. Crystallization from diisopropyl ether yields 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid; freezing point 130-131°C.

5-[4-(5-Fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleroylamino] phthalide



255 mg of 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid in 3 ml of dimethylacetamide is mixed at 0°C with 0.105 ml of thionyl chloride, stirred for 30 min at 0°C and for 45 min at room temperature, and combined with 300 mg of 5-amino phthalide. After 16 h at room temperature, the preparation is mixed with 2 M hydrochloric acid and ethyl acetate, and the organic phase is washed with water to neutrality, dried (Na_2SO_4), and evaporated. Chromatography on kieselgel with hexane/ethyl acetate (3:2) and recrystallization from diisopropyl ether yields 80 mg of 5-[4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleroylamino] phthalide; freezing point 200-201°C.

6-[4-(5-Fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



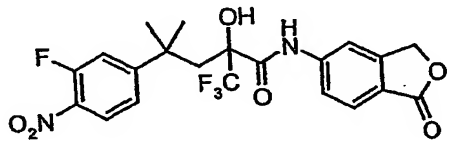
Obtained in a manner analogous to that described for Example 4 from 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleric acid and 6-amino-2,3-benzoxazine-1-one; freezing point 208-210°C.

Example 6

4-(3-Fluoro-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleric acid

Obtained in the form of an oil from 4-(3-fluoro-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleric acid ethyl ester in a manner analogous to that described under Example 4 for 4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleric acid.

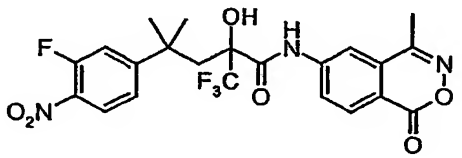
5-[4-(3-Fluoro-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide



Obtained in a manner analogous to that described for Example 4 from 4-(3-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleric acid and 5-aminophthalide; freezing point 188-189°C.

Example 7

6-[4-(3-Fluoro-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



Obtained in a manner analogous to that described for Example 4 from 4-(3-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-

trifluoromethylvaleric acid and 6-amino-2,3-benzoxazine-1-one; freezing point 236-237°C.

Example 8

6-[4-(2-Bromo-4-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

Precursors:

3-Methyl-2-butenoic acid (4-fluorophenyl) amide

A solution of 10.0 g (0.1 mol) of 3-methyl-2-butenoic acid in 200 ml of tetrahydrofuran is mixed at 0°C with 9.4 ml (0.1 mol) of chloroformic acid ethyl ester and 14.1 ml (0.1 mol) of triethylamine. After 10 min at room temperature, 10.6 ml (0.11 mol) of 4-fluoroanaline is added. The preparation is stirred for 1 h at room temperature, diluted with water, and extracted with glacial acetic acid (1 L). The organic phase is washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The residue is purified on a column chromatograph using kieselgel with hexane/ethyl acetate. Yield: 18.8 g.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.92 (d, 3H), 2.25 (d, 3H), 5.71 (sept, 1H), 7.02 (t, 2H), 7.13 (br., 1H), 7.5 (br., 2H).

3,4-Dihydro-4,4-dimethyl-6-fluoro-2-quinolone

9.4 g (48.7 mmol) of 3-methyl-2-butenoic acid (4-fluorophenyl) amide is heated to 130-140°C and mixed portionwise with 9.6 g (73.5 mmol) of aluminum chloride. After the addition has been completed, the temperature is kept at 80°C for another 30 min. The preparation is allowed to cool to room temperature and is treated carefully with 60 ml of ice water. After the addition of 150 ml of chloroform, the preparation is stirred for 15 min, rendered acid with dilute hydrochloric acid, and extracted with

chloroform (3 x 150 ml). The combined organic extracts are washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 6.0 g.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.34 (s, 6H), 2.48 (s, 2H), 6.80 (dd, 1H), 6.88 (td, 1H), 7.02 (dd, 2H), 9.02 (br., 1H)

1-*tert*-Butoxycarbonyl-3,4-dihydro-4,4-dimethyl-6-fluoro-2-quinolone
A solution of 6.0 g (30.9 mmol) of 3-4-dihydro-4,4-dimethyl-6-fluoro-2-quinolone in 200 ml of tetrahydrofuran is mixed with 8.8 g (40.2 mmol) of di-*tert*-butyldicarbonate and 4.9 g (40.2 mmol) of DMAP. After 24 h at room temperature, the preparation is evaporated, and the residue is purified by column chromatography using kieselgel and hexane/ethyl acetate. Yield: 9.0 g.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.34 (s, 6H), 1.61 (s, 9H), 2.50 (s, 2H), 6.91 (m, 2H), 7.03 (dd, 1H).

3-(2-*tert*-Butoxycarbonylamino-5-fluorophenyl)-3-methyl-1-butanol
375 ml (0.75 mol) of an aqueous solution of 2 M lithium hydroxide solution is added to a solution of 44 g (0.15 mol) of 1-*tert*-Butoxycarbonyl-3,4-dihydro-4,4-dimethyl-6-fluoro-2-quinolone in 1 L of tetrahydrofuran. After 24 h at room temperature, the preparation is evaporated, adjusted to pH 4 with 10% citric acid, and extracted with ether. The combined organic phases are washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 34.0 g of 3-(2-*tert*-butoxycarbonylamino-5-fluorophenyl)-3-methylbutyric acid [^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.62 (br.s, 15 H), 2.77 (s, 2H), 6.41 (br., 1H), 6.93 (td, 1H), 7.07 (dd, 1H), 7.20 (br. 1H)], which is dissolved in 1 L of tetrahydrofuran and mixed at 0°C with 17 ml (121 mmol) of triethylamine and 11.5 ml (121 mmol) of

chloroformic acid ethyl ester. After 10 min at 0°C, 20.7 g (546 mmol) of sodium borohydride is added, and 1 L of methyl alcohol is added slowly by drops. The preparation is stirred at 0°C for another 30 min, evaporated, diluted with acetic acid, washed with saturated NaCl solution, dried (Na_2SO_4), and purified by column chromatography using kieselgel and hexane/ethyl acetate. Yield: 6.7 g.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.40 (s, 6 H), 1.51 (s, 9H), 2.06 (t, 2H), 3.49 (q, 2H), 6.32 (br.s, 1H), 6.91 (ddd, 1H), 7.05 (dd, 1H), 7.28 (br., 1H).

2,2-Dimethylpropionic acid [3-(2-amino-5-fluorophenyl)-3-methyl]butyl ester

A solution of 6.7 g (22.7 mmol) of 3-(2-*tert*-butoxycarbonylamino-5-fluorophenyl)-3-methyl-1-butanol in 200 ml of pyridine is mixed at 0°C with 5.6 ml of pivaloyl chloride. After 24 h at room temperature, water is added and the preparation is stirred for 2 h at room temperature. The preparation is diluted with acetic acid, washed with 10% citric acid, water, saturated $NaHCO_3$, and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate acid yields 9.0 g of 2,2-dimethylpropionic acid [3-(2-*tert*-butoxycarbonylamino-5-fluorophenyl)-3-methyl]butyl ester. 6.1 g (16 mmol) of this compound is dissolved in 100 ml of dichloromethane and mixed with 30 ml of trifluoro acetic acid. After 30 min at room temperature, the preparation is diluted with acetic acid, washed with water, saturated $NaHCO_3$, and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 1.6 g.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.12 (s, 9H), 1.52 (s, 6H), 2.41 (t, 2H), 3.88 (t, 2H), 6.79 (ddd, 1H), 7.12 (dd, 1H), 7.53 (dd, 1H).

3-(2-Bromo-5-fluorophenyl)-3-methylbutanol

At -20°C, a solution of 1.97 g (5.7 mmol) of 2,2-dimethyl-propionic acid [3-(2-amino-5-fluorophenyl)-3-methyl]butyl ester in 20 ml of toluene is mixed with 11.9 ml (14.3 mmol) of a 1.2 M diisobutyl aluminum hydride toluene solution. After 30 min at -20°C, the preparation is cooled to -70°C and mixed with 4 ml of isopropanol and 6 ml of water. After 2 h at room temperature, the preparation is filtered and the filtrate is evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate acid yields 1.25 g of product.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.52 (s, 6H), 2.37 (t, 2H), 3.45 (q, 2H), 6.80 (ddd, 1H), 7.12 (dd, 1H), 7.54 (dd, 1H).

2-[1-Benzoyl-3-(2-bromo-5-fluorophenyl)-3-methylbutyl]furan

A solution of 1.0 g (3.8 mmol) of 3-(2-bromo-5-fluorophenyl)-3-methylbutanol in 24 ml of dichloromethane is treated with 8.5 ml of DMSO, 2.66 ml (19.2 mmol) of triethylamine, and 1.23 g (7.7 mmol) of pyridine/sulfur trioxide complex. After 1 h at room temperature, the preparation is mixed with 30 ml of saturated NH_4Cl and, after 15 min, extracted with 400 ml of ether. The extract is washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The residue (1.1 g) is dissolved in 8 ml of tetrahydrofuran and added at -70°C over 30 min to a solution of 2-furyllithium in 38 ml of tetrahydrofuran, which is prepared from 0.85 ml of furan (11.5 mmol) and 7.7 ml (12.3 mmol) of a 1.6 M nBuLi/hexane solution according to A. Dondoni et al., J. Org. Chem. 1997, **62**, 5484. After 1.5 h at -70°C, the preparation is poured onto 50 ml of saturated NH_4Cl and extracted with 400 ml of MTBE. The organic phase is dried (Na_2SO_4) and evaporated under vacuum. The residue (1.1 g) is dissolved in 40 ml of pyridine and then mixed with 0.9 ml (7.7 mmol) of benzoyl chloride at 0°C. After 2 h at 0°C and 2 h at room temperature,

30 mg of DMAP is added, and after another 2 h at room temperature, another 0.9 ml (7.7 mmol) of benzoyl chloride is added. After 18 h at room temperature, the preparation is mixed with 3 ml of water and evaporated under vacuum. The residue is taken up in 400 ml of MTBE, and the resulting solution is washed with 10% citric acid and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 1.46 g of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.52 (s, 3H), 1.58 (s, 3H), 2.53 (dd, 1H), 3.33 (dd, 1H), 6.10 (dd, 1H), 6.26 (m, 2H), 6.49 (ddd, 1H), 6.97 (dd, 1H), 7.34 (m, 4H), 7.48 (m, 1H), 7.81 (m, 2H).

2-Benzoyl-4-(2-bromo-5-fluorophenyl)-4-methylvaleric acid methyl ester

A suspension of 10.9 g (50.8 mmol) of sodium periodate in 140 ml of water/acetonitrile/tetrachloromethane (4:2:1) is mixed with 45 mg (0.34 mmol) of ruthenium(IV) oxide hydrate. After 10 min, a solution of 2-[1-benzoyl-3-(2-bromo-5-fluorophenyl)-3-methylbutyl]furan in 40 ml of acetonitrile is added. The preparation is stirred for another 10 min and then poured onto 400 ml of saturated Na_2SO_3. The pH is adjusted to 5 with 20% citric acid, and the preparation is extracted with acetic acid. The combined extracts are dried (Na_2SO_4) and evaporated under vacuum. The residue is taken up in 8 ml of DMF and treated with 0.42 ml (6.8 mmol) of methyl iodide and 2.21 g (6.8 mmol) of cesium carbonate. After 5 h at room temperature, the preparation is diluted with 600 ml of MTBE, washed with 10% sulfuric acid and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 0.9 g of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.58 (s, 3H), 1.62 (s, 3H), 2.55 (dd, 1H), 3.10 (dd, 1H), 3.72 (s, 3H), 5.21 (dd, 1H), 6.58 (ddd, 1H), 7.03 (dd, 1H), 7.35-7.47 (m, 3H), 7.55 (m, 1H), 7.83 (m,

2H).

4-(2-Bromo-5-fluorophenyl)-2-hydrox-4-methylvaleric acid methyl ester

A solution of 0.9 g (2.13 mmol) of 2-benzoyl-4-(2-bromo-5-fluorophenyl)-4-methylvaleric acid methyl ester in 50 ml of methyl alcohol is mixed with 1.47 g (10.6 mmol) of potassium carbonate and stirred for 3 h at room temperature. The preparation is adjusted to pH 3 with 10% sulfuric acid and extracted with acetic acid. The combined extracts are washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The residue is taken up in 8 ml of DMF and stirred at room temperature for 3 h with 1.92 g (5.9 mmol) of cesium carbonate and 0.38 ml (5.9 mmol) of methyl iodide. The preparation is mixed with 10% citric acid and extracted with MTBE. The organic phase is washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 250 mg of product.

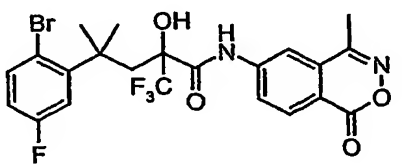
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.57 (s, 3H), 1.61 (s, 3H), 2.10 (dd, 1H), 2.51 (d, 1H), 2.82 (dd, 1H), 3.74 (s, 3H), 3.96 (ddd, 1H), 6.81 (ddd, 1H), 7.22 (dd, 1H), 7.55 (dd, 2H).

6-[4-(2-Bromo-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one

663 mg (1.56 mol) of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane, cf. D.B. Dess, J.C. Martin, J. Am. Chem. Soc. 1992, **113**, 7277) is added to a solution of 250 mg (0.78 mmol) of 4-(2-bromo-5-fluorophenyl)-2-hydrox-4-methylvaleric acid methyl ester in 10 ml of dichoromethane. After 1.5 h at room temperature, the preparation is diluted with 150 ml of MTBE, washed with a solution of 1.2 g

of $NaHCO_3$ and 4.0 g of Na_2SO_4 in 50 ml of water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The residue (250 mg) is taken up in 16 ml of Tetrahydrofuran/ethyl alcohol (1:1) and mixed with 3.9 ml (3.9 mmol) of a 1 M potassium hydroxide solution. After 30 min, the preparation is concentrated under vacuum, diluted with 20 ml of water, and washed with MTBE. The aqueous phase is adjusted to pH 2 with 10% sulfuric acid and extracted with 100 ml of acetic acid and 100 ml of dichloromethane. The combined extracts are dried (Na_2SO_4), and evaporated under vacuum. 0.06 ml (0.92 mmol) of thionly chloride is added dropwise at -6°C to the solution of the residue (230 mg) in 5 ml of dimethylacetamide. After 20 min at -6°C, 201 mg (1.14 mmol) of 6-amino-4-methyl-2,3-benzoxazine-1-one is added. The preparation is stirred for 15 h at room temperatur, rendered acid with 50 ml of 10% citric acid, and precipitated with 150 ml of MTBE. The organic phase is washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 290 mg of product.
^{1}H-NMR ([D]$_6$-DMSO), delta (ppm) = 1.57 (s, 6H), about 2.5 (s, 3H; below the DMSO signal), 3.89 (s, 2H), 7.03 (ddd, 1H), 7.34 (dd, 1H), 7.62 (dd, 1H), 8.25 (d, 1H), 8.33 (m, 2H), 11.03 (br., 1H); MS (Cl) m/z = 461, 463 (M^+).

<u>6-[4-(2-Bromo-5-fluorophenyl)-2-hydroxy-4-methyl-2-triflouromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one</u>



0.23 ml (1.25 mmol) of trifluoromethyl(trimethyl)silane and 256

mg (0.79 mmol) of cesium carbonate are added at 0°C to a solution of 290 mg (0.63 mmol) of 6-[4-(2-bromo-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one in 7 ml of DMF. After 24 h, the same amount of silane and base are added, and the preparation is stirred for another 24 h at room temperature. The preparation is diluted with 150 ml of acetic acid, washed with water and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatographic purification of the residue on kieselgel yields 230 mg of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.55 (s, 3H), 1.63 (s, 3H), 3.10 (br.s, 1H), 6.63 (ddd, 1H), 7.11 (dd, 1H), 7.40 (dd, 1H), 7.62 (dd, 1H), 8.14 (d, 1H), 8.33 (d, 1H), 8.52 (br.s, 1H);
MS (CL) m/z = 531, 533 (M^+).

Example 9

6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluoromethyl-valeroylamino]-4-methyl-2,3-benzoxazine-1-one

Precursors:

4-(1-Hydroxy-1-methylethyl)indan

10 ml (14 mmol) of a 1.4 M methyl magnesium bromide solution in toluene/tetrahydrofuran (3:1) is added dropise at 0°C to a solution of 1.6 g (10 mmol) of 4-acetylindan (F. Dallacker, J. Van Wersch, Chem. Ber. 1972, **105**, 2565). After 30 min at 0°C and 1.5 h at room temperature, the preparation is diluted with 200 ml of acetic acid, washed with 1 M hydrochloric acid and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 0.64 g of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.64 (s, 6H), 1.74 (s, 1H), 2.07 (pent, 2H), 2.90 (t, 2H), 3.16 (t, 2H), 7.11-7.19 (m, 2H), 7.29

(m 1H).

6-[4-(Indan-4'-yl)-4-methyl-2-oxovaleric acid

0.63 g (3.4 mmol) of 4-(1-hydroxy-1-methylethyl)indan is combined with 0.96 g (5.1 mmol) of 2-trimethylsiloxyacrylic acid ethyl ester (H. Sugimura, K. Yoshida, Bull. Chem Soc. Jpn. 1992, 65, 3209) in 20 ml of dichloromethane and treated at -70°C with 0.31 ml (2.6 mmol) of tin(IV) chloride. After 20 min at -70°C, the preparation is poured into 50% concentrated potassium carbonate solution and extracted with acetic acid. The combined extracts are washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The result is 0.89 g of an oil that is dissolved in 30 ml of ethyl alcohol/tetrahydrofuran (2:1) and reacted with 12.8 ml (12.8 mmol) of 1 M NaOH. After 2 h at room temperature, the preparation is evaporated under vacuum, and the residue is taken up in 30 ml of water. The aqueous phase is washed with ether and rendered acid with 50 ml of 1 M hydrochloric acid. Extraction with acetic acid, drying (Na_2SO_4), and evaporation yields 0.64 g of acid.

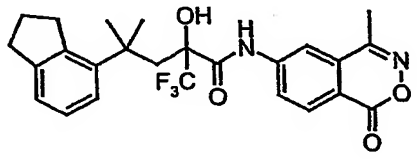
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.52 (s, 6H), 2.07 (pent, 2H), 2.85 (t, 2H), 3.08 (t, 2H), 3.42 (s, 2H), 5.02 (br.), 7.04-7.17 (m, 3H).

6-[4-(Indan-4'-yl)-4-methyl-2-oxovalerylamino]-4-methyl-2,3-benzoxazine-1-one

0.63 g (2.6 mmol) of 6-[4-(indan-4'-yl)-4-methyl-2-oxovaleric acid and 0.69 g (3.9 mmol) of 6-amino-4-methyl-2,3-benzoxazine-1-one are transformed as described for Example 1 to yield 0.31 g of product.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.56 (s, 6H), 2.08 (pent, 2H), 2.59 (s, 3H), 2.83 (t, 2H), 3.12 (t, 2H), 3.52 (s, 2H), 7.07-7.17 (m, 3H), 7.72 (dd, 1H), 8.20 (d, 1H), 8.36 (d, 1H), 8.87 (br.s, 1H).

6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroyl-amino]-4-methyl-2,3-benzoxazine-1-one



In a manner anlogous to that described for Example 1, 0.31 g (0.77mmol) of 6-[4-(indan-4'-yl)-4-methyl-2-oxovalerylamino]-4-methyl-2,3-benzoxazine-1-one is mixed with 0.56 ml (3.1 mol) of trifluomethyl(trimethyl)silane and 626 mg (1.9 mmol) of cesium carbonate in 9 ml of DMF. Column chromatography on kieselgel with hexane/ethyl acetate yields 90 mg of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.47 (s, 3H), 1.49 (s, 3H), 2.11 (m, 2H), 2.62 (s, 3H), 2.76-2.92 (m 4H), 2.96 (s, 1H), 3.17 (t, 2H), 7.14 (m, 4H), 7.63 (dd, 1H), 8.28 (d, 1H), 8.35 (d, 1H) 8.88 (br.s, 1H);
MS (Cl) m/z =475 (MH^+)

Separation of the enantiomers from Example 9:
The enantiomer mixture from Example 9 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (95:5, vol/vol). In this way, the following are obtained from 830 mg of racemate:

(-) 6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluoromethyl-valeroylamino]-4-methyl-2,3-benzoxazine-1-one as the first fraction: 310 mg [MS (Cl) m/z = 475 (MH^+), alpha $_D$ = -55.7° (c = 0.5 in tetrahydrofuran)] and
(+) 6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluoromethyl-valeroylamino]-4-methyl-2,3-benzoxazine-1-one as the second fraction: 280 mg [freezing point 196-197°C, alpha $_D$ = +55.7° (c =

0.5 in tetrahydrofuran)]

Example 10

6-[4-(5-Fluoro-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

2-Benzoyl-4-(5-fluoro-2-vinylphenyl)-4-methylvaleric acid methyl ester

A solution of 0.53 g (1.25 mmol) of 2-benzoyl-4-(2-bromo-5-fluorophenyl)-4-methyl valeric acid methyl ester and 77 mg (0.07 mmol) of tetrakis(triphenylphospine) palladium in 40 ml of toluene are heated with vinyl(tributyl)stannane for 8 h with refluxing. Evaporation and column chromatography on kieselgel with hexan/acetic acid yields 320 mg of product.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.51 (s, 3H), 1.55 (s, 3H), 2.44 (dd, 1H), 2.66 (dd, 1H), 3.70 (s, 3H), 5.14 (dd, 1H), 5.33 (dd, 1H), 5.43 (dd, 1H), 6.77 (td, 1H), 6.97 (dd, 1H), 7.22-7.33 (m, 2H) 7.48 (m, 2H), 7.55 (m, 1H), 7.80 (d, 2H).

4-(5-Fluoro-2-vinylphenyl)-2-hydroxy-4-methylvaleric acid methyl ester

Prepared in a manner analogous to that described for Example 8.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.48 (s, 3H), 1.55 (s, 3H), 1.98 (dd, 1H), 2.46 (dd, 1H), 2.50 (d, 1H), 3.70 (s, 3H), 3.96 (ddd, 1H), 5.28 (dd, 1H), 5.41 (dd, 1H), 6.90 (td, 1H), 7.12 (dd, 1H), 7.25 (dd, 1H), 7.33 (dd, 1H).

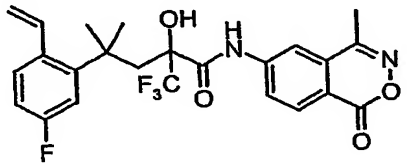
6-[4-(5-Fluoro-2-vinylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one

Prepared in a manner analogous to that described for Example 8.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.56 (s, 6H), 2.58 (s, 3H), 3.65 (s, 2H), 5.28 (dd, 1H), 5.34 (dd, 1H), 6.91 (td, 1H), 7.13 (dd,

1H), 7.20-7.30 (m, 2H), 7.78 (dd, 1H), 8.22 (d 1H), 8.35 (d, 1H), 8.98 (br., 1H).

6-[4-(5-Fluoro-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



Prepared in a manner analogous to that described for Example 8.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.47 (s, 3H), 1.54 (s, 3H), 2.60 (s, 3H), 2.87 (m, 3H), 5.45 (dd, 1H), 5.50 (dd, 1H), 6.85 (td, 1H), 7.06 (dd, 1H), 7.25-7.37 (m, 2H), 7.67 (dd, 1H), 8.18 (d, 1H), 8.34 (d, 1H), 8.73 (br.s, 1H);
MS (ES+) m/z = 479 (MH^+)

Example 11
6-[-2-hydroxy-4-methyl-2-trifluoromethyl-4-(trifluoromethyl-phenyl)valeroylamino]-4-methyl-2,3-benzoxazine-1-one2

2-Methyl-2-(4-trifluoromethylphenyl)propionitrile
A solution of 6.80 g (41.4 mmol) of 4-fluorobenzo trifluoride in 250 ml of toluene is mixed at 0°C with 124 ml (62 mmol) of a 0.5 M potassium hexamethyl disilazide/tetrahydrofuran solution and 9.44 g (137 mmol) of isobutyric acid nitrile. The preparation is stirred for 4 h at 60°C and, after cooling with water, diluted with acetic acid. The organiz phase is separated off, washed with 10% Na_2SO_4 solution and saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexan/acetic acid yields 7.68 mg of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.76 (s, 6H), 7.62 (d 2H), 7.68 (d,

2H).

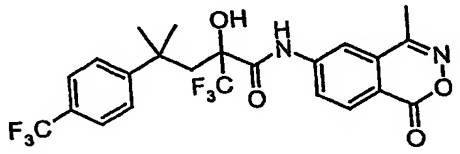
4-Methyl-4-(4-trifluoromethylphenyl)-2-pentetic acid ethyl ester
A solution of 7.6 g (36 mmol) of 2-methyl-2-(4-trifluoromethylphenyl)propionitrile in 250 ml of toluene is mixed at -70°C with 57 ml (68 mmol) of a 1.2 M diisobutyl aluminum hydride/toluene solution. After 1 h at -70°C, 10% tartaric acid is added dropwise, and the mixture is stirred for 15 min at room temperature. The preparation is diluted with ether, the organic phase is separated off, washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Yield: 7.96 g of raw 2-methyl-2-(4-trifluoromethylphenyl)propione aldehyde. 2.05 g (9.25 mmol) of this compound is dissolved in 6 ml of DME and added dropwise to a solution prepared from 3.10 g (13.9 mmol) phosphono acetic acid triethyl ester and 0.55 g (13.9 mmol) of 60% sodium hydride in 12 ml of DME. After 1 h at room temperature, the preparation is mixed with saturated NH_4Cl and diluted with ethyl acetate and water. The phases are separated, the aqueous phase is extracted with ethyl acetate, and the combined organic extracts are washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The residue is purified on kieselgel with hexane/ethyl acetate. Yield: 1.72 g of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.30 (t, 3H), 1.49 (s, 6H), 4.21 (q, 2H), 5.82 (d, 1H), 7.10 (d, 1H), 7.43 (d, 2H), 7.59 (d, 2H).

2-Hydroxy-4-methyl-4-(4-trifluoromethylphenyl)valeric acid ethyl ester
1.72 g (6.0 mmol) of 4-methyl-4-(4-trifluoromethylphenyl)-2-pentetic acid ethyl ester is stirred for 15 h in the ethyl acetate in the presence of 0.17 g of 10% palladium/activated charcoal catalyst in a hydrogen atmospere (1 atm). The preparation is filtered over Celite and evaporated under vacuum.

Yield: 1.72 g 4-methyl-4-(4-trifluoromethylphenyl)valeric acid ethyl ester. 0.57 g (2.0 mmol) of this compound is dissolved in 7 ml of tetrahydrofuran and treated at -78°C with 5.6 ml (2.8 mmol) of potassium hexamethyl disilazide/toluene solution. After 25 min, 0.73 g (2.8 mmol) of 3-phenyl-2-phenylsulfonyloxaziridine (F.A. Davis, S. Chattopadhyay, J.C. Towson, S. Lal, T. Reddy J. Org. Chem 1988, **53**, 2087) in 7 ml of tetrahydrofuran is added dropwise, and the mixture is stirred for 30 min at -78°C. The preparation is mixed with saturated NH_4Cl and warmed to room temperature over 1 h. The tetrahydrofuran is removed under vacuum, the residue is taken up in ether, the solid is filtered off, the phases are separated, and the aqueous phase is extracted with ether. The combined organic phases are washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on kieselgel with hexane/ethyl acetate yields 0.24 mg of product.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.26 (t, 3H), 1.42 (s 3H), 1.50 (s, 3H), 1.90 (dd, 1H), 2.10 (br., 1H), 2.24 (dd, 1H), 3.94 (dd, 1H), 4.15 (m, 2H), 7.53 (d, 2H), 7.60 (d, 2H).

6-[4-Methyl-2-oxo-4-(4-trifluoromethylphenyl)valeroylamino]-4-methyl-2,3-benzoxazine-1-one
Prepared in a manner analogous to that described for Example 8.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.53 (s, 6H), 2.58 (s, 3H), 3.47 (s, 2H), 7.50 (d, 2H), 7.58 (d, 2H), 7.78 (dd, 1H), 8.21 (d, 1H), 8.35 (d, 1H), 8.98 (br., 1H);
MS (Cl) m/z = 433 (MH^+)

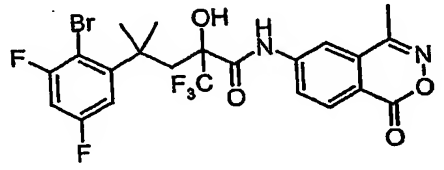
6-[2-Hydroxy-4-methyl-2-trifluoromethyl-4-(4-trifluoro-methylphenyl)valeroylamino]-4-methyl-2,3-benzoxazine-1-one



Prepared in a manner analogous to that described for Example 8. ^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.47 (s, 3H), 1.50 (s, 3H), 2.53 (d, 1H), 2.58 (s, 3H), 2.91 (s, 1H), 2.95 (d, 1H), 7.55 (s, 4H), 7.62 (dd, 1H), 8.18 (d 1H), 8.33 (d, 1H), 8.73 (br.s, 1H); MS (ES+) m/z =503 (MH^+)

Example 12

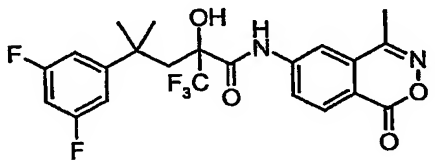
6-[4-(2-Bromo-3,5-difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



Prepared in a manner analogous to that described for Example 8. ^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.56 (s, 3H), 1.64 (s, 3H), 2.58 (s, 3H), 3.00 (d, 1H), 3.22 (d, 1H), 3.31 (br.s, 1H), 6.58 (td, 1H), 6.97 (dt, 1H), 7.64 (dd, 1H), 8.11 (d, 1H), 8.34 (d, 1H), 8.43 (br.s, 1H).

Example 13

6-[4-(3,5-difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



Example 13 is a byproduct of the synthesis of Example 12.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.41 (s, 3H), 1.44 (s, 3H), 2.44 (d, 1H), 2.60 (s, 3H), 2.80 (br.s, 1H), 2.89 (d, 1H), 6.53 (tt, 1H), 6.92 (m, 2H), 7.66 (dd, 1H), 8.24 (d, 1H), 8.35 (d, 1H), 8.70 (br.s, 1H).

Example 14

6-[4-(5-Fluoro-2-trifluoromethylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

2-(5-Fluoro-2-trifluoromethylphenyl)acetonitrile

1.95 g (30 mmol) of potassium cyanide is added to a solution of 5.14 g (20 mmol) of 5-fluoro-2-trifluoromethylbenzyl bromide in 45 ml of ethanol/8 ml of water and stirred for 64 h at room temperature. The reaction solution is diluted with ethyl acetate and extracted with saturated sodium hydrogen carbonate solution. The organic phase is washed with water, dried, and evaporated. The remaining residue is purified by bulb tube distillation and recrystallized. Yield: 3.6 g (89%). Freezing point: 41-42°C.

2-(5-Fluoro-2-trifluoromethylphenyl)-2-methylpropionitrile

In a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionitrile, 2-(5-fluoro-2-trifluoromethylphenyl)-2-propionitrile is obtained as a colorless

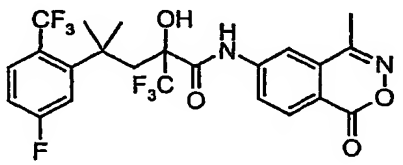
oil. Boiling point 90°C/0.04 hPa.

2-(5-Fluoro-2-trifluoromethylphenyl)-2-methylpropionaldehyde
In a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde, 2-(5-fluoro-2-trifluoromethylphenyl)-2-methylpropionaldehyde is obtained as a colorless oil. Boiling point 80°C/0.05 hPa.

4-(5-Fluoro-2-trifluoromethylphenyl)-4-methyloxovaleric acid
In a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyloxovaleric acid, 4-(5-fluoro-2-trifluoromethylphenyl)-4-methyloxovaleric acid is obtained as a viscous oil.

6-[4-(5-Fluoro-2-trifluoromethylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one
6-[4-(5-Fluoro-2-trifluoromethylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one is synthesized in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one.
^{1}H-NMR ($CDCl_3$ + DMSO), delta (ppm) = 1.47 (s, 6H), 2.44 (s, 3H), 3.59 (s, 2H), 6.92 (dt, 1H), 7.33 (dd, 1H), 7.61 (dd, 1H), 8.03 (dd, 1H), 8.16 (d, 1H), 8.30 (d, 1H), 10.34 (bs, 1H).

6-[4-(5-Fluoro-2-trifluoromethylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



6-[4-(5-Fluoro-2-trifluoromethylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one is synthesized in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.42 (s, 3H), 1.55 (s, 3H), 2.56 (d, 1H), 2.57 (s, 3H), 2.91 (d, 1H), 3.28 (bs, 1H), 6.85 (dt, 1H), 7.32 (dd, 1H), 7.56-7.66 (m, 2H), 8.13 (d, 1H), 8.34 (d, 1H), 8.51 (bs, 1H);
MS (EI) m/z = 520 (M^+)

Separation of the enantiomers from Example 14:
The enantiomer mixture from Example 14 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (19:1, vol/vol). In this way, the following are obtained from 100 mg of racemate:

(-) 6-[4-(5-Fluoro-2-trifluoromethylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the first fraction: 40 mg [freezing point 162-165°C, alpha $_D$ = -45.5° (c = 0.5 in tetrahydrofuran)] and

(+) 6-[4-(5-Fluoro-2-trifluoromethylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the second fraction: 38 mg [freezing point 160-165°C]

The compounds in Table 4 are obtained in a manner analogous to that described for Example 14.

Trifluoromethyl compounds:

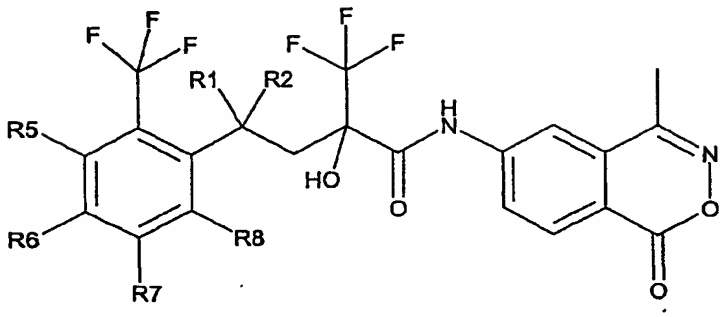


Table 4: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	R1 / R2	Fp. [°C]	Isomerie bzw $[\alpha]_D$
1	H	H	H	H	CH_3	154-156	Racemat
2	H	H	H	H	CH_3	164-170	-72,8
3	H	H	H	H	CH_3	188-190	+69,0
4	H	F	H	H	CH_3	170-172	Racemat
5	H	F	H	H	CH_3	173-175	-67,5
6	H	F	H	H	CH_3	174-177	(+)-Form
7	H	H	F	H	CH_3	170	Racemat
8	H	H	F	H	CH_3	162-166	-45,5
9	H	H	F	H	CH_3	160-165	(+)-Form
10	H	H	Cl	H	CH_3	172	Racemat
11	H	H	Cl	H	CH_3	178-181	-143,1
12	H	H	Cl	H	CH_3	180-182	(+)-Form

Example 15

6-[2-Hydroxy-4-methyl-2-trifluoromethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazine-1-one

2-Methyl-2-(1-naphthyl)-propionitrile
A solution of 16.7 g (100 mmol) of 1-naphthylacetonitrile in 200 ml of DMF and 15 ml (240 mmol) of methyl iodide is mixed at 0°C with 10.4 g (260 mmol) of sodium hydride (addition over 2.5 h). The preparation is stirred for 3 h at 0°C and 18 h at 25°C and then mixed with ice and ethyl acetate. The organic phase is rendered acid with 10% H_2SO_4, washed three times with water, dried (Na_2SO_4), and evaporated under vacuum. A partial purification is achieved by bulb tube distillation (boiling range 60-130°C) under oil-pump vacuum. Yield: 18.8 g.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 2.00 (s, 6H), 7.41-7.60 (m, 3H), 7.64 (ddd, 1H), 7.87 (d br., 1H), 7.93 (dd, 1H), 8.55 (d, 1H).

4-Methyl-4-(1-naphthyl)-2-pentetic acid ethyl ester
In a manner analogous to that described for 4-methyl-4-(4-trifluoromethylphenyl)-2-pentetic acid ethyl ester from Example 11, 7.62 g of the product is obtained from 8.81 g (45.1 mmol) of 2-methyl-2-(1-naphthyl)-propionitrile.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.25 (t, 3H), 1.70 (s, 6H), 4.16 (q, 2H), 5.73 (d, 1H), 7.38-7.50 (m, 4H), 7.53 (dd, 1H), 7.78 (d, 1H), 7.81-7.89 (m, 1H), 8.00-8.08 (m, 1H).

2-Hydroxy-4-methyl-4-(1-naphthyl)valeric acid ethyl ester
In a manner analogous to that described for 2-hydroxy-4-methyl-4-(4-trifluoromethylphenyl)valeric acid ethyl ester from Example 11, 3.52 g of the product is obtained from 7.62 g (28.4 mmol) of 4-methyl-4-(1-naphthyl)-2-pentetic acid ethyl ester.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.14 (t, 3H), 1.72 (s, 3H), 1.74

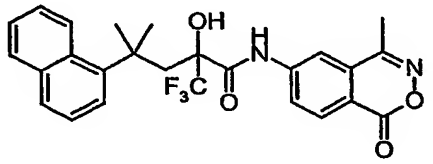
(s, 3H), 2.27 (dd, 1H), 2.52 (dd, 1H), 2.76 (dd, 1H), 3.95-4.08 (m, 3H), 7.38-7.51 (m, 3H), 7.57 (d, 1H), 7.75 (d, 1H), 7.88 (dd, 1H), 8.40 (d, 1H).

6-[4-Methyl-2-oxo-4-(1-naphthyl)valeroylamino]-4-methyl-2,3-benzoxazine-1-one

In a manner analogous to that described for Example 11, 861 mg of the product is obtained.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.59 (s, 3H), 1.78 (s, 6H), 2.57 (s, 3H), 3.88 (s, 2H), 7.44 (m, 2H), 7.54 (m, 2H), 7.69 (dd, 1H), 7.75 (d br., 1H), 7.87 (dd, 1H), 8.15 (d, 1H), 8.32 (d, 1H), 8.46 d br., 1H).

6-[2-Hydroxy-4-methyl-2-trifluoromethyl-4-(1-naphthyl)-valeroylamino-4-methyl-2,3-benzoxazine-1-one



Prepared in a manner analogous to that described for Example 8.

Yield: 77.1 mg of the product.

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.57 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 2.54 (s, 2H), 3.10 (d, 1H), 3.23 (d, 1H), 5.30 (s, 2H), 7.25-7.38 (m, 2H), 7.46 (dd, 1H), 7.51 (d, 1H), 7.60 (m, 2H), 7.76 (d, 1H), 7.97 (d br., 1H), 8.24 (d, 1H), 8.42 (d, 1H).

Example 16

6-[3-{1-(2-Chlorophenyl)cyclopropyl}-2-hydroxy-2-trifluoromethylpropionyl]amino-4-methyl-2,3-benzoxazine-1-one

Precursors:

1-(2-Chlorophenyl)cyclopropane carbonitrile

A solution of 13.1 g of 2-chlorophenylacetonitrile and 20.3 g of 1,2-dibromopropane in 142 ml DMF is mixed at room temperature with 9 g of sodium hydride (55-56% in oil). The preparation is stirred for several hours and then carefully added to water. Extraction with ethyl acetate and filtration through kieselgel yields 13.1 g of the desired product.

MS (ei): $M^{(+)}$ = 177

1-(2-Chlorophenyl)-1-cyclopropane carbaldehyde

13.1 g of 1-(2-chlorophenyl)-1-cyclopropane carbaldehyde [Translator's note: perhaps this should read "1-(2-chlorophenyl)-cyclopropane carbonitrile."] in 116 ml of toluene is mixed dropwise at -70°C with 64.5 ml of diisobutyl aluminum hydride. After 4 h at -70°C, 343 ml of ethyl acetate is added, and the mixture is allowed to come to room temperature overnight. Water and ethyl acetate are added, and the preparation is filtered through kieselguhr, washed in ethyl acetate solution with water, dried (Na_2SO_4), and evaporated. Flash chromatography on kieselgel with hexane/ethyl acetate (8:2) yields 9.7 g of the product.

MS (ei): $M^{(+)}$ = 180

2-Ethoxy-3-[1-(2-chlorophenyl)-1-cyclopropyl]acrylic acid ethyl ester

14.3 g of phosphonate in 40 ml of tetrahydrofuran is mixed at 0°C with 29 ml of lithium diisopropylamide, and the mixture is stirred for 20 min at 0°C. 9.7 g of 1-(2-chlorophenyl)-1-cyclopropane carbaldehyde in 40 ml of tetrahydrofuran is added dropwise. After 24 h at room temperature, the preparation is mixed with water, extracted with ethyl acetate, washed with ethyl acetate solution with water, and dried (Na_2SO_4). Evaporation yields 15.5 g of the product.

MS (ei): $M^{(+)}$ = 294

2-Ethoxy-3-[1-(2-chlorophenyl)-1-cyclopropyl]acrylic acid
15.4 g of 2-ethoxy-3-[1-(2-chlorophenyl)-1-cyclopropyl]acrylic acid ethyl ester in 350 ml of sodium hydroxide solution (ethanol/water, 2:1) is stirred for 24 h at room temperature. The solvent is distilled off, the residue is divided between water and diethyl ether, the water solution is rendered acid with 2 N hydrochloric acid, and extraction is performed with diethyl ether. Washing of the organic phase with water, drying (Na_2SO_4), and evaporation yields 11.2 g of the product.
MS (ei): $M^{(+)}$ = 294

3-[1-(2-Chlorophenyl)-1-cyclopropyl]-2-oxopropionic acid
11.2 g of 2-ethoxy-3-[1-(2-chlorophenyl)-1-cyclopropyl]acrylic acid in 230 ml of 1 M sulfuric acid and 42 ml of concentrated acetic acid is stirred for 24 h at 110°C. Water is added to the preparation, and it is extracted with ethyl acetate and washed with ethyl acetate solution with water. Drying (Na_2SO_4), and evaporation yields 10.7 g of the product.
MS (ei): $M^{(+)}$ = 238
^{1}H-NMR ($CDCl_3$), alpha (ppm) = 0.98 (m, 4H), 3.28 (s, 2H), 7.13-7.22 (m, 2H), 7.29-7.35 (m, 1H), 7.43-7.49 (m, 1H).

6-{3-[1-(2-Chlorophenyl)cyclopropyl]-2-oxopropionylamino}-4-methyl-2,3-benzoxazine-1-one
10.7 g of 3-[1-(2-chlorophenyl)-1-cyclopropyl]-2-oxopropionic acid in 175 ml of dimethylacetamide is mixed at -5°C with 4.1 ml of thionyl chloride and stirred for 20 min. Then, 5.0 g of MBO solid is added. After 20 h at room temperature, water and ethyl acetate are added, and the preparation is washed with water, dried (Na_2SO_4), and evaporated. Chromatography on kieselgel with hexane/ethyl acetate (0%-30%) yields 9.6 g of the product.

MS (ei): $M^{(+)}$ = 397

6-[3-{1-(2-Chlorophenyl)cyclopropyl}-2-hydroxy-2-trifluoromethylpropionyl]amino-4-methyl-2,3-benzoxazine-1-one

9.5 g of 6-{3-[1-(2-chlorophenyl)cyclopropyl]-2-oxopropionyl-amino}-4-methyl-2,3-benzoxazine-1-one in 140 ml of methylformamide is mixed at 0°C with 16.9 ml of trifluoromethyltrimethylsilane and 9.65 g of cesium carbonate. After 24 h at room temperature, a spatula tip of tetrabutyl ammonium fluorohydrate is added, and the preparation is stirred for 30 min, mixed with water and ethyl acetate, washed with ethyl acetate with water, dried (Na_2SO_4), and evaporated. Chromatography on kieselgel with hexane/ethyl acetate (0%-30%) yields 2.98 g of the product. Freezing point: 195-196°C.

Separation of the enantiomers from Example 16:

The enantiomer mixture from Example 16 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (19:1, vol/vol). In this way, the following are obtained from 2.68 mg of racemate:

(-) 6-[3-{1-(2-Chlorophenyl)cyclopropyl}-2-hydroxy-2-trifluoromethylpropionyl]amino-4-methyl-2,3-benzoxazine-1-one as the first fraction: 1.3 g [freezing point 233-235°C, alpha $_D$ = -81.4° (c = 0.5 in chloroform)] and

(+) 6-[3-{1-(2-Chlorophenyl)cyclopropyl}-2-hydroxy-2-trifluoromethylpropionyl]amino-4-methyl-2,3-benzoxazine-1-one as the second fraction: 1.25 g [freezing point 238-240°C

In a manner analogous to that described for Example 16, the compounds in Tables 5-8 are obtained.

Chlorine compounds:

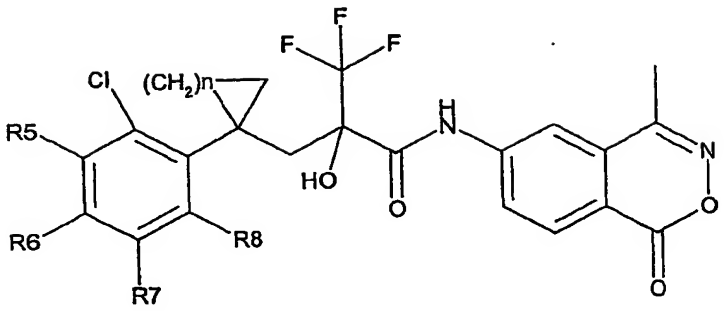


Table 5: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	n =	Fp. [°C]	Isomerie bzw $[\alpha]_D$
1	H	H	H	H	2	231-233	-47,1
2	H	H	H	H	2	230-232	(+)-Form
3	H	H	H	H	3	195-197	-70,5
4	H	H	H	H	3	202-203	(+)-Form
5	H	F	H	H	1	228-230	Racemat
6	H	F	H	H	1	218-219	-88,6
7	H	F	H	H	1	217-219	(+)-Form
8	H	F	H	H	2	212-214	Racemat
9	H	F	H	H	2	236-238	+74,2
10	H	F	H	H	2	235-237	-75,0
11	H	H	F	H	1	196	Racemat
12	H	H	F	H	1	239-240	-95,4
13	H	H	F	H	1	239-240	(+)-Form
14	H	H	F	H	2	222-223	Racemat
15	H	H	F	H	2	247-249	77,6
16	H	H	F	H	2	247-249	+79,6
17	H	Cl	H	H	1	235-239	-81,6
18	H	Cl	H	H	1	199-201	(+)-Form
19	H	Cl	H	H	2	232	-46,7
20	H	Cl	H	H	2	232-234	(+)-Form

Trifluoromethyl compounds:

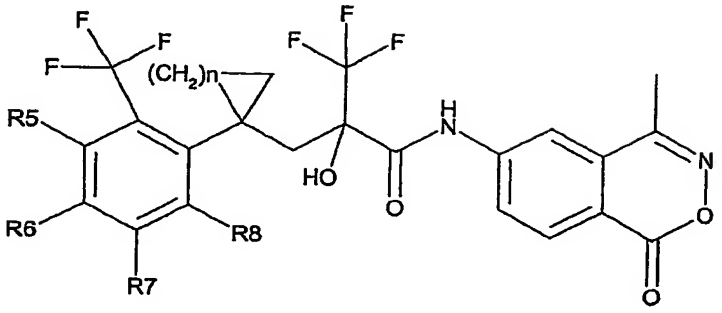


Table 6: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	n =	Fp. [°C]	Isomerie bzw $[\alpha]_D$
21	H	H	H	H	1	205	Racemat
22	H	H	H	H	1	222-223	-96,5
23	H	H	H	H	1	219-221	(+)-Form
24	H	H	H	H	2	218-222	Racemat
25	H	H	H	H	2	220-221	-16,4
26	H	H	H	H	2	220-222	(+)-Form
27	H	H	H	H	4	150-153	Racemat
28	H	H	F	H	1	242-245	Racemat
29	H	H	F	H	1	235-246	-40,1
30	H	H	F	H	1	244-246	(+)-Form
31	H	H	F	H	2	241-244	Racemat
32	H	H	F	H	2	242-244	-82,7
33	H	H	F	H	2	242-244	(+)-Form

Fluorine compounds:

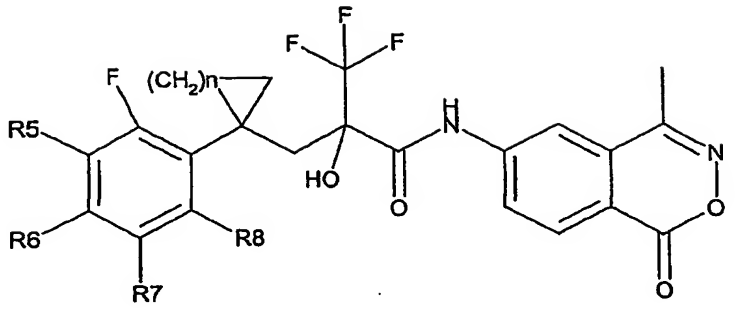


Table 7: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	n =	Fp. [°C]	Isomerie bzw $[\alpha]_D$
34	H	H	H	H	1	215-216	Racemat
35	H	H	H	H	1	260-262	-113,3
36	H	H	H	H	1	260-263	(+)-Form
37	H	H	H	H	2	190-191	Racemat
38	H	H	H	H	2	198-201	-103,4
39	H	H	H	H	2	207-209	+103
40	H	H	H	H	3	168-171	-117,6
41	H	H	H	H	3	167-170	+112,3
42	H	H	H	H	4	90-93	Racemat
43	H	H	H	H	4	178-184	-105
44	H	H	H	H	4	185-187	+102,6
45	F	H	H	H	1	230-232	Racemat
46	F	H	H	H	1	238-250	-106,3
47	F	H	H	H	1	254-256	(+)-Form
48	F	H	H	H	2	182-185	Racemat
49	H	H	F	H	1	198-199	Racemat
50	H	H	F	H	1	240	-130,2
51	H	H	F	H	1	241	(+)-Form
52	F	H	F	H	1	215	Racemat
53	F	H	F	H	2	205	Racemat

Bromine compounds:

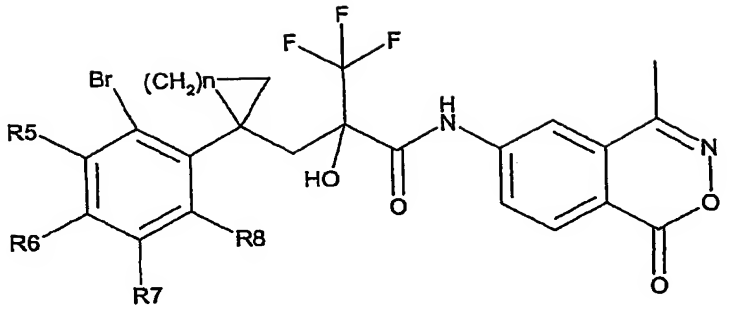


Table 8: [Key: Verbindung = Compound; Fp. = freezing point; Isomerie bzw = Isomerism and]; Racemat = Racemate]

Verbindung	R5	R6	R7	R8	n =	Fp. [°C]	Isomerie bzw $[\alpha]_D$
54	H	H	H	H	1	196-200	Racemat
55	H	H	H	H	1	239-241	-56,6
56	H	H	H	H	1	240-241	+56,0

Example 17

6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

Precursors:

2-Methyl-2-(3-methyl-2-nitrophenyl)propionitrile

2-Methyl-2-(3-methyl-2-nitrophenyl)propionitrile is synthesized

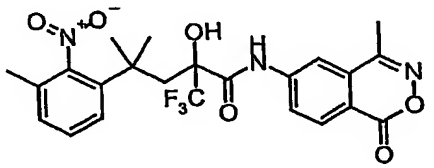
in a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionitrile. Boiling point 140°C/0.05 hPa.

2-Methyl-2-(3-methyl-2-nitrophenyl)propionaldehyde
2-Methyl-2-(3-methyl-2-nitrophenyl)propionaldehyde is synthesized in a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde. Boiling point 140°C/0.05 hPa.

4-Methyl-4-(3-methyl-2-nitrophenyl)-2-oxovaleric acid
In a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid, 4-methyl-4-(3-methyl-2-nitrophenyl)-2-oxovaleric acid is obtained as an oil.

6-[4-Methyl-4-(3-methyl-2-nitrophenyl)-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one
6-[4-Methyl-4-(3-methyl-2-nitrophenyl)-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one is obtained in a manner analogous to that described for 5-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino] phthalide. Freezing point: 184-187°C.

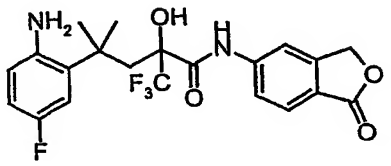
6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



Obtained in a manner analogous to that described for Example 1 from 6-[4-methyl-4-(3-methyl-2-nitrophenyl)-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one. Freezing point: 201-203°C.

Example 18

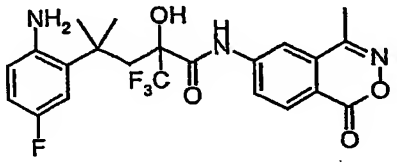
5-[4-(2-Amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide



65.8 mg of 5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide in 15 ml of methanol is reduced with hydrogen at normal pressure in 3 h in the presence of palladium/charcoal (10%), vacuum filtered over kieselguhr, and evaporated. Recrystallization from ethyl acetate/diisopropyl ether yields 51 mg of 5-[4-(2-amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide. Freezing point 174°C.

Example 19

6-[4-(2-Amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

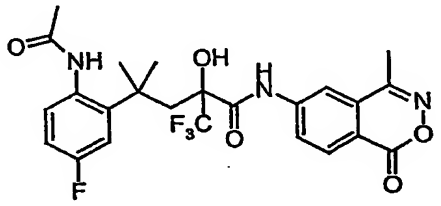


42 mg of 6-[4-(5-fluoro-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one is dissolved in 1 ml of acetic acid and 1 ml of tetrahydrofuran b, mixed with 22.5 mg of iron powder, and stirred for 16 h at room temperature. The preparation is vacuum filtered over kieselguhr and evaporated, and the residue is taken up in ethyl acetate and

washed with a saturated sodium hydrogen carbonate solution. Chromatography on kieselgel with hexane/ethyl acetate (1.5:1) and recrystallization from diisopropyl ether yields 10 mg of 6-[4-(2-amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one. Freezing point: 208°C.

Example 20

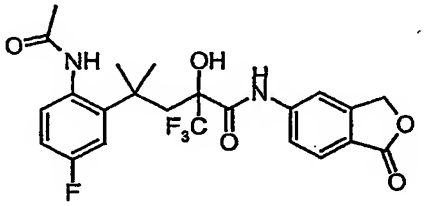
6-[4-(2-Acetylamino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



9.4 mg of 6-[4-(2-Amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one and 0.04 ml of acetic acid anhydride in 0.5 ml of tetrahydrofuran is stirred for 2 days at room temperature and mixed with ethyl acetate and sodium hydrogen carbonate solution. The ethyl acetate solution is dried and evaporated. Chromatography on kieselgel yields 8 mg of 6-[4-(2-acetylamino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one. MS (ei): $M^{(+)}$ = 510

Example 21

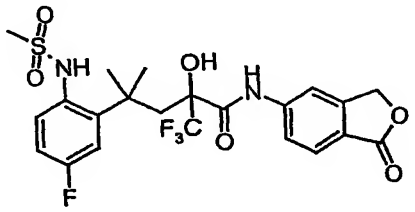
5-[4-(2-Acetylamino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide



Is obtained in a manner analogous to that described for Example 20 from 5-[4-(2-amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide. Freezing point 125°C.

Example 22

5-[4-(5-Fluoro-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide



17.7 mg of 5-[4-(2-amino-5-fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino] phthalide, 0.4 ml of pyridine, and 0.078 ml of mesyl chloride are stirred for 17 h at room temperature, mixed with ethyl acetate, and washed three times with 1 N hydrochloric acid. The ethyl acetate solution is dried and evaporated. Chromatography on kieselgel with ethyl acetate/hexane (1:1) yields 11 mg of 5-[4-(5-fluoro-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-valeroylamino] phthalide. Freezing point 218°C.

Example 23

6-[4-(2-Bromo-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

Obtained from 6-[4-(2-bromo-3-methoxyphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one in a manner analogous to that described for Example 3. MS (esi): $M^{(+)} + 1 =$ 543 (^{79}Br) and 545 (^{81}Br)

Separation of the enantiomers from Example 23:

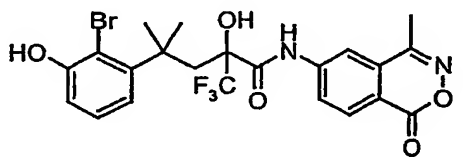
The enantiomer mixture from Example 23 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (93:7, vol/vol). In this way, the following are obtained from 200 mg of racemate:

(-) 6-[4-(2-Bromo-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the first fraction: 86 mg [freezing point 233-235°C, alpha $_D$ = --81.4° (c = 0.5 in chloroform)] and

(+) 6-[4-(2-Bromo-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one as the second fraction: 82 mg

Example 24

(+) 6-[4-(2-Bromo-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one

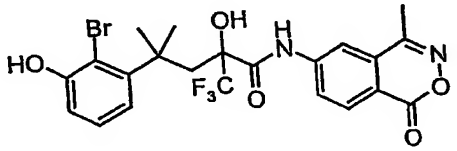


78 mg of (+) 6-[4-(2-bromo-3-methoxyphenyl)-2-hydroxy-4-methyl-2-

trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one is mixed at 0°C with 0.71 ml of a 1 molar solution of boron tribromide in dichloromethane. After 2 h of stirring at 0°C, the mixture is added to water and extracted with ethyl acetate. The organic phase is dried (Na_2SO_4) and evaporated. Trituration of the residue with hexane yields the title compound in crystalline form. Freezing point 226-231°C, alpha $_D$ = +91.1° (c = 0.5 in chloroform)

Example 25

(-) 6-[4-(2-Bromo-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one



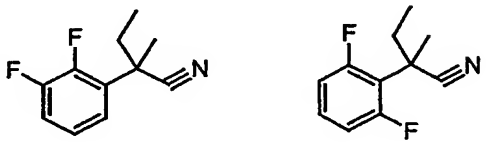
Example 25 is produced in a manner analogous to that described for Example 24 from the corresponding (-) 6-[4-(2-bromo-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-valeroylamino]-4-methyl-2,3-benzoxazine-1-one. Freezing point 227-231°C, alpha $_D$ = -94.3° (c = 0.5 in chloroform)

Example 26

6-[4-(2,3-Difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-caproylamino]-4-methyl-2,3-benzoxazine-1-one

Precursors:

2-Methyl-2-(2,3-difluorophenyl)butyronitrile and 2-Methyl-2-(2,6-difluorophenyl)butyronitrile



A solution of 5.0 g (37.85 mmol) of 1,2,3-trifluorobenzene, 3.30 g (39.74 mmol) of 2-methylbutylnitrile, and 75.7 ml (0.5 M in toluene) of potassium-*bis*-trimethylsilylamide in 182 ml of toluene is heated for 3 h at 60°C. The solution is mixed with ice water and ether. The organic phase is rendered acid with 10% H_2SO_4, washed three times with water, dried (Na_2SO_4), and evaporated under vacuum. Chromatography on kieselgel with 0-4% ether/hexane yields 3.8 g 2-methyl-2-(2,3-difluorophenyl)-butyronitrile and 1.6 g of 2-methyl-2-(2,6-difluorophenyl)-butyronitrile.

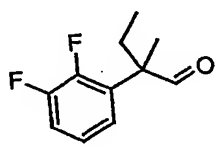
2-Methyl-2-(2,3-difluorophenyl)butyronitrile:

^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.88 (t, 3H), 1.81 (s, 3H), 1.95-2.1 (m, 1H), 2.1-2.25 (m, 1H), 7.05-7.2 (m, 2H), 7.3-7.4 (m, 1H).

2-Methyl-2-(2,6-difluorophenyl)butyronitrile:

^{1}H-NMR ($CDCl_3$), delta (ppm) = 1.06 (t, 3H), 1.89 (t, 3H), 1.95-2.1 (m, 1H), 2.15-2.3 (m, H), 6.85-6.95 (m, 2H), 7.2-7.3 (m, 1H).

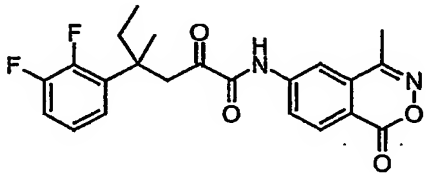
2-(2,3-Difluorophenyl)-2-methylbutyraldehyde



2-(2,3-Difluorophenyl)-2-methylbutyraldehyde is obtained as a

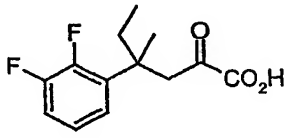
colorless oil in a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.79 (t, 3H), 1.41 (s, 3H), 1.85-2.0 (m, 1H), 2.0-2.15 (m, 1H), 7.0-7.3 (m, 3H), 9.68 (d, 1H).

4-(2,3-Difluorophenyl)-4-methyl-2-oxocaproic acid



4-(2,3-Difluorophenyl)-4-methyl-2-oxocaproic acid is obtained in a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.71 (t, 3H), 1.47 (s, 3H), 1.7 (m, H), 2.0 (m, 1H), 3.26 (d, 1H), 3.74 (d, 1H), 6.9-7.1 (m, 3H).

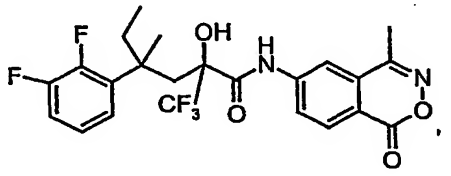
6[4-(2,3-Difluorophenyl)-4-methyl-2-oxocaproylamino]-4-methyl-2,3-benzoxazine-1-one



6[4-(2,3-Difluorophenyl)-4-methyl-2-oxocaproylamino]-4-methyl-2,3-benzoxazine-1-one is obtained in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.73 (t, 3H), 1.5 (s, 3H), 1.7 (m,

1H), 2.05 (m, 1H), 2.58 (s, 3H), 3.37 (d, 1H), 3.84 (d, 1H), 7.0 (m, 3H), 7.72 (dd, 1H), 8.24 (d, 1H), 8.33 (d, 1H), 9.0 (bs, 1H).

6-[4-(2,3-Difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-caproylamino]-4-methyl-2,3-benzoxazine-1-one



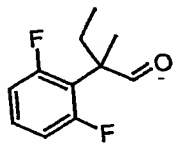
6-[4-(2,3-Difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-caproylamino]-4-methyl-2,3-benzoxazine-1-one is obtained in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one. The diastereomer mixture is separated on kieselgel with 20-100% ethyl acetate/hexane:
Diastereomer 1: ^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.66 (t, 3H), 1.39 (s, 3H), 1.7 (m, 1H), 2.1 (m, 1H), 2.61 (s, 3H), 2.7 (m, 2H), 6.9-7.2 (m, 3H), 7.67 (dd, 1H), 8.31 (d, 1H), 8.37 (d, 1h), 8.8 (s, 1H).
Diastereomer 2: ^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.62 (t, 3H), 1.59 (s, 3H), 1.6 (m, 1H), 2.15 (m, 1H), 2.23 (d, 1H), 2.55 (s, 3H), 3.07 (d, 1H), 6.58 (m, 1H), 6.71 (m, 1H), 6.92 (m, 1H), 7.46 (dd, 1H), 8.01 (d, 1H), 8.27 (d, 1H), 8.3 (s, 1H).

Example 27

6-[4-(2,6-Difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-caproylamino]-4-methyl-2,3-benzoxazine-1-one

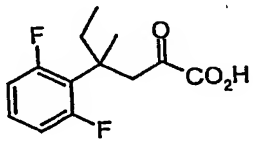
Precursors:

2-(2,6-Difluorophenyl)-2-methylbutyraldehyde



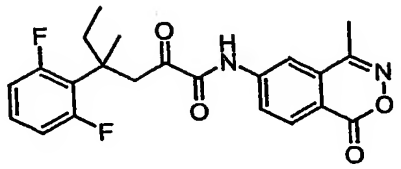
2-(2,6-Difluorophenyl)-2-methylbutyraldehyde is obtained as a colorless oil in a manner analogous to that described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.83 (t, 3H), 1.49 (t, 3H), 1.9-2.1 (m, 2H), 6.85-6.95 (m, 2H), 7.2-7.3 (m, 1H), 9.69 (t, 1H).

4-(2,6-Difluorophenyl)-4-methyl-2-oxocaproic acid



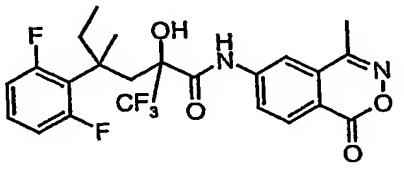
4-(2,6-Difluorophenyl)-4-methyl-2-oxocaproic acid is obtained in a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleric acid.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.76 (t, 3H), 1.62 (t, 3H), 1.7 (m, H), 1.9 (m, 1H), 3.0 (dt, 1H), 4.0 (d, 1H), 6.8 (m, 2H), 7.13 (m, 1H).

6[4-(2,6-Difluorophenyl)-4-methyl-2-oxocaproylamino]-4-methyl-2,3-benzoxazine-1-one



6[4-(2,6-Difluorophenyl)-4-methyl-2-oxocaproylamino]-4-methyl-2,3-benzoxazine-1-one is obtained in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.81 (t, 3H), 1.64 (t, 3H), 1.77 (m, 1H), 1.96 (m, 1H), 2.5 (s, 3H), 3.12 (dt, 1H), 4.09 (d, 1H), 6.8 (m, 2H), 7.15 (m, 1H), 7.77 (dd, 1H), 8.30 (d, 1H), 8.34 (d, 1H), 9.1 (bs, 1H).

6-[4-(2,6-Difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-caproylamino]-4-methyl-2,3-benzoxazine-1-one



6-[4-(2,6-Difluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-caproylamino]-4-methyl-2,3-benzoxazine-1-one is obtained as a diastereomer mixture in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one.
^{1}H-NMR ($CDCl_3$), delta (ppm) = 0.7 (m, 3H), 1.4 (m, 1H), 1.5, 1.7, (2t, 3H), 2.0-3.2 (m, 6H), 6.4-7.3 (m, 3H), 7.4-8.4 (m, 3H), 8.5,

8.9 (2bs, 1H).

Example 28

6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-hydroxy-2-trifluoromethylpropionyl]amino}-4-methyl-2,3-benzoxazine-1-one

Precursors:

4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-carbonitrile

6.76 g of (2-chloro-5-fluorophenyl)acetonitrile and 5.7 ml of 2,2'-dichlorodiethyl ether are dissolved in 100 ml of dimethylformamide and mixed under ice cooling with 3.7 g of sodium hydride (60%). After 3 h at 0°C and 16 h at room temperature, the preparation is mixed with ice water and ethyl acetate and rendered acid with 1 M hydrochloric acid, and the ethyl acetate phase is washed with water, dried (Na_2SO_4), and evaporated. Chromatography on kieselgel yields 6.2 g of 4-(2-chloro-5-fluorophenyl)-4-pyranylcarbonitrile [translator's note: this is not the same compound as the title compound (see boldface above)]. Freezing point 91-93°C.

4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-carbaldehyde

4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-carbaldehyde is obtained as a colorless oil in the manner described for 2-(5-fluoro-2-methylphenyl)-2-methylpropionaldehyde. Boiling point 145°C/0.04 hPa.

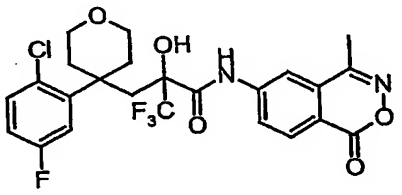
3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]oxopropionic acid

3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]oxopropionic acid is obtained in a manner analogous to that described for 4-(5-fluoro-2-methylphenyl)-4-methyloxovalaric acid. Freezing point 158°C.

6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-oxopropionylamino}-4-methyl-2,3-benzoxazine-1-one

6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-oxopropionylamino}-4-methyl-2,3-benzoxazine-1-one is synthesized in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazine-1-one. Freezing point 206-208°C

6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-hydroxy-2-trifluoromethylpropionyl]amino}-4-methyl-2,3-benzoxazine-1-one



6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-hydroxy-2-trifluoromethylpropionyl]amino}-4-methyl-2,3-benzoxazine-1-one is synthesized in a manner analogous to that described for 6-[4-(5-fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoro-methylvaleroylamino]-4-methyl-2,3-benzoxazine-1-one. Freezing point 224-226°C

Separation of the enantiomers from Example 28:

The enantiomer mixture from Example 28 is separated by chromatography on a chiral carrier (CHIRALPAC AD®, DAICEL Co.) with hexane/ethanol (9:1, vol/vol). In this way, the following are obtained from 300 mg of racemate:

(-) 6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-hydroxy-2-trifluoromethylpropionyl]amino}-4-methyl-2,3-benzoxazine-1-one as the first fraction: 129 mg [freezing point 181-183°C, alpha $_D$ = -83.2° (c = 0.5 in tetrahydrofuran)] and

(+) 6-{3-[4-(2-Chloro-5-fluorophenyl)tetrahydropyran-4-yl]-2-hydroxy-2-trifluoromethylpropionyl]amino}-4-methyl-2,3-benzoxazine-1-one as the second fraction: 129 mg [freezing point 181-183°C

Example 29

In the glucocorticoid receptor (GR) binding test using cytosol preparations of Sf9 cells that had been infected with recombinant baculoviruses that code for GR and in which 10 nM [^{3}H]dexamethasone was used as the reference substance (cf. Lefebvre et al. J. Steroid. Biochem. **33**, 557-563, 1989), the compounds with formula 1 show a very high affinity for the GR (see Table 9).

Table 9: GR binding test

Compound	IC_{50} [mol/L]
Example 38	$<3.0 \times 10^{-10}$
Example 16, compound 26	1.6×10^{-8}
Example 16, compound 33	1.1×10^{-9}
Example 3, compound 9	$<3.0 \times 10^{-10}$
Example 16, compound 16	6.2×10^{-10}
Example 16, compound 13	$<3.0 \times 10^{-10}$
Dexamethasone	2.8×10^{-8}
Prednisolone	4.0×10^{-8}

Example 30

The potency of the anti-inflammatory effect is measured on the basis of the inhibition of the secretion of cytokine IL-8 in a cell test. The compounds pursuant to the invention with general formula I inhibit lipopolysaccharide (LPS)-induced secretion of cytokine IL-8 in the human THP-1 monocyte cell line. The concentration of the cytokine was determined in the supernatant by means of commercially available ELISA kits. The compounds with formula 1 show a high to very high potency and efficacy in their inhibition (see Table 10).

Table 10: IL-8 values

Compound	Inhibition of IL-8 secretion IC_{50} [mol/L]	Inhibition of IL-8 secretion Efficacy
Example 38	8.6×10^{-9}	56
Example 16, compound 26	4.3×10^{-9}	77
Example 16, compound 33	3.0×10^{-8}	45
Example 3, compound 9	6.5×10^{-8}	51
Example 16, compound 16	1.0×10^{-8}	80
Example 16, compound 13	9.6×10^{-9}	58
Prednisolone	2.4×10^{-8}	95

Example 31

The anti-inflammatory activity of the compounds with general formula I was tested on croton oil-induced inflammation in rats and mice [J. Exp. Med. (1995), **182**, 99-108]. In these experiments, the croton oil was applied topically in ethanolic solution to the ears of the animals. The test compounds were administered topically or systemically at the same time as or 2 hours before the croton oil. After 16-24 hours, the weight of the ears was used as the measure of inflammatory edema. The compounds with formula 1 showed a standard (comparable to prednisolone) or greater than standard inhibition of croton oil-induced inflammation (see Table 11).

Table 11: Inhibition of edema formation

Compound	Inhibition of edema [%] with 3 mg/kg	Inhibition of edema [%] with 30 mg/kg
Example 38	58	101
Example 16, compound 26	11	81
Example 16, compound 33	77	86
Example 3, compound 9	50	92
Example 16, compound 16	54	78
Example 16, compound 13	47	106
Prednisolone	35	84

Example 32

As the parameter for the side effects of the steroid-induced catabolic metabolism, the activity of the enzyme tyrosine amino transferase (TAT) was determined photometrically in liver homogenates. This activity is a good measure of the undesired metabolic effects of the glucocorticoids. To measure TAT induction, the animals were killed 8 hours after administration of the test compounds, their livers were removed, and the TAT activity in the homogenate was measured. In this test, anti-inflammatory doses of the compounds with general formula I induced the TAT only slightly or not at all relative to steroids (Table 12).

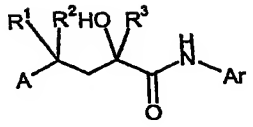
Table 12: Induction of tyrosine amino transferase activity

Compound	Induction factor* for TAT with 3 mg/kg	Induction factor* for TAT with 30 mg/kg
Example 38	1.2	6.0
Example 16, compound 26	1.4	3.7
Example 16, compound 16	1.3	2.0
Prednisolone	2.6	8.0

*The induction factor stands for the n-fold increase of the TAT activity in treated animals relative to untreated animals.

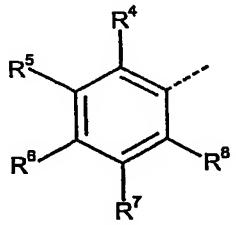
Patent Claims

1. Use of compounds with general formula I



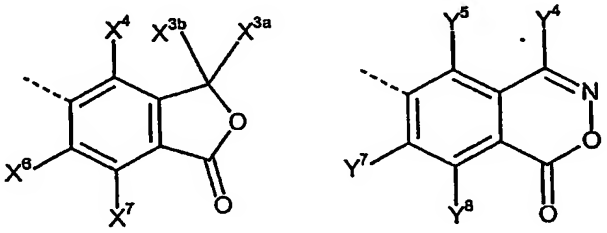
(I)

where R^1 and R^2 are alike or different and stand for a hydrogen atom, a C_1-C_5 alkyl group or, together with the C atom of the chain, for a ring with a total of three to seven members, and R^3 stands for a straight-chained or branched C_1-C_5 alkyl group or a straight-chained or branched, partially or completely fluorinated C_1-C_5 alkyl group.
A stands for the following group (the dashed line indicates the point of attachment),



where R^4 to R^8 are the same or different and stand for a hydrogen atom, a halogen atom, a cyano group, a nitro group, or $COOR^9$ group, where R^9 stands for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group or a benzyl group, a $CONR^{10}$ group, where R^{10} stands for a hydrogen atom or a straight-chained or branched C_1-C_5 alkyl group, an NHR^{11} group, where R^{11} can stand for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched, partially or completely fluorinated C_1-C_5 alkyl group, a C_1-C_5 acyl group, an $SO_2(C_1$-$C_5)$ alkyl group or an SO_2-phenyl group that likewise has been substituted by a halogen or a C_1-C_5 alkyl group.

R^4 to R^8 can also stand for a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched C_2-C_5 alkenyl group, a straight-chained or branched C_2-C_5 alkinyl group, straight-chained or branched C_1-C_5 alkyl group that has been partially or completely substituted by fluorine atoms, a C_1-C_5 acyl group, an aryl residue, or a heteroaryl residue.
R^4 and R^5, together with the two carbon atoms of the A ring, stand for a saturated or unsaturated carbocyclic ring with a total of five to seven members.
Ar stands for a ring system selected from the group with general formula 1 or 2



1 2

where the residues X^{3a}, X^{3b}, X^4, X^6, X^7 (in partial formula 1) and Y^4, Y^5, Y^7, Y^8 (in partial formula 2) are the same or different and stand for a hydrogen atom, a straight-chained or branched C_1-C_5 alkyl group, a straight-chained or branched partially or fluorinated C_1-C_5 alkyl group.

The residues X^4, X^6, X^7 (in partial formula 1) and Y^5, Y^7, Y^8 (in partial formula 2), furthermore, are the same or different and stand for a hydrogen atom, a halogen atom, a hydroxy group, a C_1-C_5 alkoxy group, or a C_1-C_5 alkanoyloxy group. They also can stand for their racemates, their separately occurring stereoisomers, and their physiologically tolerable salts for the manufacture of a medication for the treatment of inflammation.

2. Compounds with general formula I according to Claim 1

6-[4-(5-Fluor-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(5-Fluor-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-phthalid

6-[4-(2-Chlor-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(5-Fluor-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-phthalid

6-[4-(5-Fluor-2-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(3-Fluor-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-phthalid

6-[4-(3-Fluor-4-nitrophenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(Indan-4'-yl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on 6-[4-(5-Fluor-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(5-Fluor-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(5-Fluor-2-vinylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(4-trifluormethylphenyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(4-trifluormethylphenyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(4-trifluormethylphenyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(3,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(3,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(3,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Cyano-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Ethenyl-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Ethyl-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Fluor-2-phenylphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Fluor-2-(furan-2'-yl)phenyl}-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3,5-difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[2-Hydroxy-4-methyl-2-trifluormethyl-4-(1-naphthyl)-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-3-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-3-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-3-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-4-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-4-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-4-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-6-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-6-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-6-fluor-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,4-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,4-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,4-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,5-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,5-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,5-Dichlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(4-Brom-2-chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(4-Brom-2-chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(4-Brom-2-chlorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Chlor-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Chlor-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Chlor-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylhexanoylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylhexanoylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,4-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,4-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,4-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,5-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3,5-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3,5-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3,5-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2,3,4-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2,3,4-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2,3,4-Trifluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(3-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(3-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(3-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(4-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(4-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(4-Chlor-2-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Fluor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Fluor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Fluor-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Bromphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Bromphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Bromphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(2-Trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(2-Trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(4-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(4-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(4-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(5-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(5-Fluor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[4-(5-Chlor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[4-(5-Chlor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[4-(5-Chlor-2-trifluormethyl-phenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-) 6-[3-{1-(2-Chlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+) 6-[3-{1-(2-Chlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-4-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Chlor-5-fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethyl-propionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,4-Dichlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,4-Dichlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,4-Dichlorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,4-Dichlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,4-Dichlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,4-Dichlorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Trifluormethyl-phenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-) 6-[3-{1-(2-Trifluormethyl-phenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+) 6-[3-{1-(2-Trifluormethyl-phenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(5-Fluor-2-trifluormethyl-phenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl]-amino-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclopentyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Fluorphenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Fluorphenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Fluorphenyl)-cyclohexyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,3-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,3-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3-Difluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[3-{1-(2,3-Difluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[3-{1-(2,3-Difluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,5-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,5-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,5-Difluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3,5-Trifluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2,3,5-Trifluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2,3,5-Trifluorphenyl)-cyclobutyl}-2-hydroxy-2-trifluormethylpropionyl-amino]-4-methyl-2,3-benzoxazin-1-on

6-[3-{1-(2-Bromphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(-)-6-[3-{1-(2-Bromphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

(+)-6-[3-{1-(2-Bromphenyl)-cyclopropyl}-2-hydroxy-2-trifluormethylpropionylamino]-4-methyl-2,3-benzoxazin-1-on

6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[2-Hydroxy-4-methyl-4-(3-methyl-2-nitrophenyl)-2-trifluormethylvaleroylamino]-4-methyl-2,3-benzoxazin-1-on

5-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-phthalid

(-) 5-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-phthalid

(+) 5-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-phthalid

6-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4- methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4- methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Amino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylvaleroyl-amino]-4- methyl-2,3-benzoxazin-1-on

6-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4- methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4- methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4- methyl-2,3-benzoxazin-1-on

5-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(-) 5-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(+) 5-[4-(2-Acetylamino-5-fluorphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

5-[4-(5-Fluor-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(-) 5-[4-(5-Fluor-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

(+) 5-[4-(5-Fluor-2-mesylaminophenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-phthalid

6-[4-(2-Brom-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Brom-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Brom-3-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(-) 6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

(+) 6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on

6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on
(-)-6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on
(+)-6-[4-(2-Brom-3-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluormethyl-valeroylamino]-4-methyl-2,3-benzoxazin-1-on
6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on
(-) 6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on
(+) 6-[4-(2,3-Difluorphenyl)-2-hydroxy-4-methyl-2-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on
6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-4-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on
(-) 6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-4-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on
(+) 6-[4-(2,6-Difluorphenyl)-2-hydroxy-4-methyl-4-trifluormethylcaproylamino]-4-methyl-2,3-benzoxazin-1-on
6-{3-[4-(2-Chlor-5-fluorphenyl)-tetrahydropyran-4-yl]-2-hydroxy-2-trifluormethylpropionylamino}-4-methyl-2,3-benzoxazin-1-on
(-) 6-{3-[4-(2-Chlor-5-fluorphenyl)-tetrahydropyran-4-yl]-2-hydroxy-2-trifluormethylpropionylamino}-4-methyl-2,3-benzoxazin-1-on
(+) 6-{3-[4-(2-Chlor-5-fluorphenyl)-tetrahydropyran-4-yl]-2-hydroxy-2-trifluormethylpropionylamino}-4-methyl-2,3-benzoxazin-1-on

3. 2,3-Benzoxazine-1-one according to Claim 2

4. Use of the compounds with general formula I according to Claim 2 for the manufacture of medicinal products.

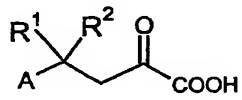
5. Use of the compounds according to Claim 2 for the manufacture a medication for the treatment of inflammation.

6. Pharmaceutical preparations containing at least one compound according to Claim 2, as well as pharmaceutically tolerable carriers.

7. Use of at least one compound with general formula I according to Claim 1 for the manufacture of medicinal products for the treatment of at least one of the diseases that for the most part are accompanied by inflammatory, allergic, and/or proliferative processes:

(i) Pulmonary diseases
(ii) Rheumatic diseases, autoimmune diseases, and diseases of the joints
(iii) Allergies
(iv) Vascular inflammation (vasculitides)
(v) Dermatologic diseases
(vi) Kidney diseases
(vii) Liver diseases
(viii) Gastrointestinal diseases
(ix) Proctologic diseases
(x) Eye diseases
(xi) Ear, nose, and throat diseases
(xii) Neurologic diseases
(xiii) Blood diseases
(xiv) Neoplastic diseases
(xv) Endocrine diseases
(xvi) Transplantations
(xvii) Severe shock conditions
(xviii) Substitution therapy in patients with adrenal insufficiency
(xix) Emesis
(xx) Pain of inflammatory etiology, e.g., lumbago

8. Methods for the manufacture of compounds with general formula I according to claims 1 and 2 characterized by the fact that they contain a alpha-ketocarbonic acid with general formula II

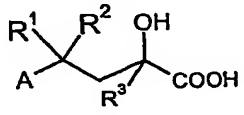


(II)

where A, R^1, and R^2 have the meanings given for formula I, is either esterified or is reacted with a compound with general formula III

$$(R^{12})_3SiR^3 \qquad (III)$$

where R^3 has the meaning given for general formula I and R^{12} stands for a C_1-C_5 alkyl group, to form a compound with general formula IV. The reaction takes place in the presence of a catalyst, such as fluoride salts, or with an alkyl metal compound, such as the Grignard reagent or a lithium alkyl.



(IV)

If desired, the ester can be cleaved again and then reacted with a compound with general formula V

$$Ar\text{-}NH\text{-}R^{13} \qquad (V)$$

where R^{13} is a hydrogen atom or a C_1-C_5 acyl group and Ar has the meaning given for general formula I. Subsequently, the R^{13}

residue is split off in order to obtain a compound with formula I or reacted directly with a compound with general formula V

$$Ar\text{-}NH\text{-}R^{13} \qquad (V)$$

where R^{13} is a hydrogen atom or a C_1-C_5 acyl group and Ar has the meaning given for general formula I, possibly after activation of the acid function by, for example, transformation to the acid chloride. Subsequently, in the desired sequence, the R^{13} residue is split off and the compound is reacted with a compound with general formula III

$$(R^{12})_3SiR^3 \qquad (III)$$

where R^3 and R^{12} have the meanings given above. The reaction takes place in the presence of a catalyst, such as fluoride salts, or with an alkyl metal compound, such as the Grignard reagent or a lithium alkyl.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 01/08501

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D265/02 C07D307/88 C07D413/12 A61K31/536 A61K31/365
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 32584 A (KALKBRENNER FRANK ;KROLIKIEWICZ KONRAD (DE); EKERDT ROLAND (DE); S) 8 June 2000 (2000-06-08) cited in the application page 1, line 19-24; claims 1,2 page 20	1-8
X	WO 98 54159 A (SCHERING AG) 3 December 1998 (1998-12-03) cited in the application claim 1; examples 1-206 page 9, line 16 -page 14, line 11 page 15 page 26, paragraph 3 page 30	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2001	12/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

INTERNATIONAL SEARCH REPORT

Information on patent family members

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